

# Profile of Inherited Neuromuscular and Movement Disorders Among Filipinos: A Referral Single-Center Retrospective Study



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## ABSTRACT

**Background:** Neuromuscular and movement disorders comprise a heterogeneous group of acquired and inherited conditions affecting the motor unit and central movement pathways. Genetic data from underserved populations, including Filipinos, remain limited, highlighting the need for population-specific characterization.

**Objective:** To characterize inherited neuromuscular and movement disorders among Filipinos and determine the diagnostic yield and genetic spectrum using next-generation sequencing (NGS).

**Methods:** This referral single-center retrospective study reviewed Filipino patients who underwent genetic testing for suspected inherited neuromuscular and movement disorders. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.

**Results:** Among 85 patients, 24 (28.2%) had pathogenic/likely pathogenic variants, 33 (38.8%) had variants of uncertain significance (VUS) and 28 (32.9%) were negative. Confirmed diagnoses

included pediatric cases of limb-girdle muscular dystrophy, Duchenne muscular dystrophy, spinal muscular atrophy and GNE-related myopathy, and adult cases with myofibrillar myopathy, spinocerebellar ataxia and amyotrophic lateral sclerosis. Pathogenic variants involved 26 genes, most commonly SMN1.

**Conclusion:** This NGS-based characterization of inherited neuromuscular and movement disorders in Filipinos showed 28% diagnostic yield and a spectrum comparable to other Asian cohorts. The high rate of VUS underscores the need for family segregation studies and careful genotype–phenotype correlation. This study highlights the critical role of genetic testing in accurate diagnosis and targeted management to improve outcomes for patients with these rare disorders.

## INTRODUCTION

Neuromuscular and movement disorders encompass various conditions that impact the muscles, neuromuscular junctions, peripheral nerves, motor neurons and the motor system. The causes of these conditions are diverse; they may be acquired or inherited. If acquired, these conditions may arise from infectious, traumatic, or toxic causes. On the other hand, these disorders may be secondary to a genetic mutation that can display autosomal recessive, autosomal dominant, or X-linked inheritance. The prominent clinical manifestation of neuromuscular disorders (NMD) is characterized

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by muscle weakness, which may be intermittent, fluctuating, or progressive and may eventually lead to severe functional disability brought about by muscle degeneration.

Worldwide, the prevalence of specific inherited NMDs and movement disorders ranges from 3.7 to 4.99 per 10,000 people. This figure can vary significantly across different populations.[1] Some specific inherited NMDs, such as Becker muscular dystrophy, facioscapulohumeral dystrophy, myotonic dystrophy and Charcot-Marie-Tooth disease, as well as inherited movement disorders such as Parkinson's disease, ataxia, tics and dystonia have shown amplified prevalence rates.[2] The increased number of these inherited neuromuscular and movement diseases were attributed to the available innovative and improved diagnostic evaluation, including genetic evaluation.

To date, there are only a few reported literature in Asia regarding the prevalence of inherited neuromuscular and movement disorders. In South Asia, the frequency of NMDs was at 91.2 per 100,000, specifically on non-dystrophin-related NMDs among the pediatric population.[3] In Hong Kong, the estimated prevalence of inherited NMDs is 1 in 7528. Of the inherited neuromuscular diseases, the most common is dystrophinopathy, followed by spinal muscular atrophy and congenital myopathy.[4] Meanwhile, in movement disorders, the incidence of Huntington's disease or chorea is lower in Asians compared to populations in Europe, North America and Australia. Hemifacial spasm (HFS) is more prevalent in Asians, with a reported rate of 12.63 per 100,000, although the number of scientific publications on the condition remains relatively small. This may be due to the ease of diagnosing and treating HFS. Studies on dystonia in Southeast Asia represent 9.4% of global research, indicating a low prevalence of dystonia in the region, with the exception of X-linked dystonia-parkinsonism (XDP), which occurs only in the Philippines.[5]

Clinical evaluation of patients with suspected hereditary NMDs usually consists of gathering a comprehensive history, conducting a thorough neurological examination alongside having neurophysiological tests such as electromyography and nerve conduction test and other adjunct procedures such as muscle biopsy.

At present, genetic testing is becoming an emerging tool that guides the diagnosis of illnesses. Recently,

there have been nearly 500 genes identified as the etiology of these diverse groups of neuromuscular and movement disorders. However, neuromuscular and movement disorders exhibit significant diversity in both their observable traits and genetic makeup: phenotypic and genotypic heterogeneity. Mutations in various genes can lead to a similar clinical progression, while a single gene mutation can manifest in a range of distinct phenotypes and still evolve.

There is a notable absence of published data regarding the prevalence of genetically confirmed inherited NMDs in the Philippines. Most patients still receive diagnoses solely based on their observable characteristics, primarily because they face challenges regarding the accessibility of genetic testing centers or are burdened by their associated costs. Moreover, only a limited number of institutions provide genetic evaluation services.

This study aims to provide substantial insights into various inherited neuromuscular and movement disorders observed in the Filipino population. It will serve to increase awareness regarding their clinical characteristics and establish genotype-phenotype correlations, which could potentially pave the way for advancements in therapeutic options.

### Primary Objective

Generally, this is the first retrospective study that would like to investigate the spectrum of inherited NMDs among the Filipino population who underwent neuromuscular profiling at the University of Santo Tomas Hospital, España Boulevard, Manila from September 2018 to June 2024.

### Specific Objectives

To obtain all the essential knowledge and data, the study sought to answer crucial questions as follows:

1. What is the diagnostic accuracy of each genetic test?
2. What are the different inherited neuromuscular diseases found among Filipinos?
3. What are the ages and genders of patients who were confirmed to have inherited neuromuscular diseases?
4. What are the expressed traits of every gene that were classified as a variant of uncertain significance?

## METHODS

This is a retrospective study of patients with clinical suspicion of hereditary neuromuscular and movement disorders seen and referred at the University of Santo Tomas Hospital Neuroscience Institute for genetic evaluation. The said center is on the second floor of the St. John Macias Building of the University of Santo Tomas Hospital situated at España Boulevard, Metro Manila, Philippines. These patients were seen as outpatients between September 2018 and June 2024 and were retrospectively included in this study.

A total of 85 patients, both pediatric and adult, were suspected to have hereditary neuromuscular disorder and movement disorder by an adult neuromuscular specialist, and they were referred to the Neuroscience Institute at the University of Santo Tomas Hospital. Fourteen individuals were excluded from this study upon initial screening based on the exclusion criteria. The specimens were sent to Centogene and Invitae located at Rostock, Germany, and San Francisco, California, respectively. NGS based panels were requested such as whole exome sequencing, whole genome sequencing, comprehensive neuromuscular and comprehensive neuropathies. The methodology adheres to STROBE guidelines, shown in Figure 1.

## INCLUSION AND EXCLUSION CRITERIA

### Inclusion Criteria

- Individuals, both pediatric and adult, who are suspected of having hereditary neuromuscular and movement disorders by clinical presentation.
- Patients were referred to the Neuroscience Institute at the University of Santo Tomas Hospital between September 2018 and June 2024.
- Patients who underwent genetic testing (whole exome sequencing, whole genome sequencing, comprehensive neuromuscular and comprehensive neuropathies panels)
- Patients evaluated by an adult neuromuscular specialist at the University of Santo Tomas Hospital with a clinical suspicion of hereditary neuromuscular and movement disorders.

### Exclusion Criteria

- Patients diagnosed with neuromuscular and movement disorders that are not inherited or genetic in nature.
- Patients whose genetic test results are incomplete or unavailable.
- Patients not referred to the University of Santo Tomas Hospital for genetic testing.
- Patients seen outside the defined study period of September 2018 to June 2024.
- Patients who, upon further investigation, are found to have a diagnosis other than hereditary neuromuscular and movement disorders.

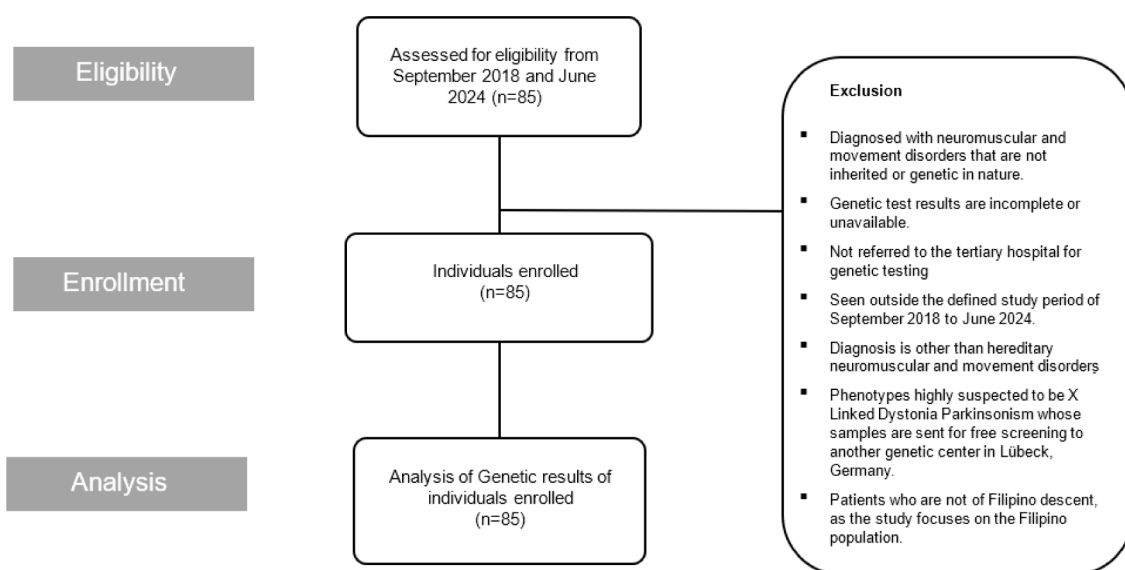


Figure 1: STROBE flow diagram

- Patients referred for reasons other than neuromuscular or movement disorders.
- Patients with phenotypes highly suspected to be x-linked dystonia Parkinsonism whose samples are sent for free screening to another genetic center in Lübeck, Germany.
- Patients who are not of Filipino descent, as the study focuses on the Filipino population.

## DATA ANALYSIS

The findings will be presented in terms of frequency and percentages for qualitative variables. The clinical accuracy of the diagnostic test, which in this study is the genetic evaluation, will be assessed by measuring the true/false positive and true/false negative of said evaluation.

## RESULTS

The genetic testing sites interpreted results in the context of clinical findings, family history and other laboratory data. The accuracy of genetic testing was determined based on the classification system of the American College of Medical Genetics and Genomics (ACMG), wherein pathogenic and likely pathogenic variants were considered positive results, likely benign and benign variants were considered negative results, and variants of uncertain significance were reported separately and interpreted in correlation with the patient's clinical findings and family history. Of the 85 patients that underwent genetic testing, 24 (28.23%) patients had positive genetic results with neuromuscular or movement disorders, while 33 (38.82%) had one or more variants of uncertain significance (VUS) and 28 (32.94%) had negative results. The diagnostic yield of next-generation sequencing (NGS) was 28.23% and the proportion of VUS was 38.82%. Notably, several rare inherited disorders were identified among patients with confirmed pathogenic variants, as seen in Table 1.

Of the 24 patients who tested positive for genetic conditions, seven are pediatric patients (6 males and 1 female) aged between 2 months and 17 years. The remaining 17 patients are adults (11 males and 6 females) ranging from 20 to 71 years old. All of

them did not report being born to consanguineous parents. In the pediatric population, the identified disorders included limb-girdle muscular dystrophy, Duchenne muscular dystrophy, spinal muscular atrophy, and GNE-related myopathy. In contrast, the adult population exhibited a broader range such as myofibrillar myopathy, Miyoshi muscular dystrophy, limb-girdle muscular dystrophy, spinal muscular atrophy, spinocerebellar ataxia, amyotrophic lateral sclerosis with frontotemporal dementia, early-onset Parkinson's disease, Wilson's disease, Charcot-Marie-Tooth disease and G6PD deficiency which presented as painful muscle spasms. The detailed clinical presentation, genotype and phenotype correlation for patients who tested positive are summarized in Table 2.

This study found mutations in 26 distinct genes as illustrated in Figure 2. The most frequent genetic alteration was observed in the SMN1 gene affecting four individuals. This was followed by mutations in Duchenne muscular dystrophy (DMD) found in three individuals and *DYS* in two individuals. Other genetic mutations involved *CAPN3*, *G6PD*, *DES*, *POLG*, *SOD1*, *POMT2*, *PRKN*, *ATXN*, *MYH7*, *SMN1*, *CPT2*, *SCN4A*, *FUS*, *DMD*, *PINK1*, *GNE*, *ATP7B*, *PMP22* and *SPG11*. The individuals confirmed to have autosomal recessive spinal muscular atrophy, characterized by pathogenic mutations in the *SMN1* gene exhibited generalized dystonia, hypotonia, progressive muscle weakness and recurrent respiratory infections. The earliest age of diagnosis in this cohort was two months. Moreover, those identified with X-linked DMD presented with progressive muscle weakness and flexion contractures.

## DISCUSSION

This study investigated the correlation of phenotypic characteristics and genotype of Filipino adult and pediatric patients presenting with neuromuscular and movement disorders. The diagnostic accuracy of genetic testing in this study was defined based on the guidelines of the ACMG.

The interpretation of genetic findings was supported by clinical correlation, family history and ancillary laboratory data providing a comprehensive

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
13	M	Muscle weakness	Pathogenic (class 1)	CAPN3	21	c.2242C>T c.145C>T	p.(Arg748*) p.(Arg49Cys)	Het Het	Stop gain Missense	LGMD2A (Limb-girdle muscular dystrophy type 2A); Autosomal recessive
49	M	Hand tremor, Parkinsonism	Uncertain significance (class 3)	PSEN2	4	c.31G>A	p.(Glu11Lys)	Het	Missense	Alzheimer's disease type 4; Autosomal dominant
69	M	Gait disturbance; Polyneuropathy, Short stature	Uncertain significance (class 3)	MYH2	30	c.4094G>A	p.(Arg1365Lys)	Het	Missense	Congenital myopathies (proximal myopathy, ophthalmoplegia); Autosomal dominant
47	M	Hyperkinesia, Intermittent painful muscle spasms, Muscle stiffness, Myotonia	Pathogenic (class 1)	G6PD	9	c.961G>A	p.(Val321Met)	Hem	Missense	Glucose-6-phosphate dehydrogenase deficiency
71	F	Muscle weakness	Pathogenic (class 1)	DES	7	c.1285C>T	p.(Arg429*)	Het	Stop gain	Myofibrillar myopathy type 1, Autosomal dominant and recessive Kaiser-type neurogenic scapulohumeral syndrome, Autosomal dominant Dilated cardiomyopathy type 1; Autosomal dominant
17	M	Proximal muscle weakness, Flexion contracture	Pathogenic (class 1)	DMD	62	c.9204_9207del	p.(Asn3068Lysfs*20)	Hem	Frameshift	Duchenne muscular dystrophy; X-linked
20	M	Distal lower limb muscle weakness, Waddling gait	Pathogenic (class 1)	DYSF	42	c.4551G>A	p.(Trp1517*)	Hom	Stop gain	Miyoshi muscular dystrophy 1; Autosomal recessive

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
56	F	Ataxia, Bowel incontinence, Dysarthria, Dysphagia	Uncertain significance (class 3)	FGF4	5	c.664A>G	p.(Thr222Ala)	Het	Missense	Spinocerebellar ataxia type 27 (SCA27); Autosomal dominant
64	F	Bradykinesia, Hyposmia, Memory impairment, Rigidity, Tremor	Likely pathogenic (class 2)	POLG	21	c.3358_3361dup	p.(Glu1121Valfs*2)	Het	Frameshift	Mitochondriopathy
23	M	Gait disturbance, Impaired vibration sensation, Muscle weakness, Myalgia	Uncertain significance (class 3)	HADHA	6	c.556C>A	p.(Gln186Iys)	Hom	Missense	Trifunctional protein deficiency, Autosomal recessive LCHAD deficiency, Autosomal recessive
54	F	Tremors; Scanning speech; Spasticity	Uncertain significance (class 3)	PRKCG	4	c.310C>T	p.(Arg104Cys)	Het	Missense	Spinocerebellar ataxia type 14 (SCA14); Autosomal dominant
57	M	Bradykinesia, Dystonia, Hypomimic face, Tremors, Rigidity	Uncertain significance (class 3)	EIF4G1	4	c.108_113dup	p.(Gln37_Ala38dup)	Het	In-frame	Parkinson disease, type 18; Autosomal dominant
49	M	Hyperreflexia; Hypertonia; Muscle weakness; Parkinsonism; Spasticity	Pathogenic (class 1)	SOD1	5	c.434T>C	p.(Leu145Ser)	Het	Missense	Amyotrophic lateral sclerosis type 1; Autosomal dominant or recessive
58	F	Truncal ataxia; Behavioral abnormality; Depression; Dysarthria; Speech impairment	Uncertain significance (class 3) Uncertain significance (class 3) Uncertain significance (class 3)	SYNE1 SYNE1	9 113	c.598G>A c.20737C>T	p.(Val200Ile) p.(Arg6913Cys)	Het Het	Missense Missense	Variant of uncertain significance Spinocerebellar ataxia 8; Autosomal recessive Myogenic-type arthrogyrosis multiplex congenita; Autosomal recessive Emery-Dreifuss muscular dystrophy 4; Autosomal dominant

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
29	M	Dysphagia; Exercise-induced muscle cramps; Fasciculations; Fatigable weakness; Fatigable weakness of swallowing muscles; Gynecomastia; Muscle spasm; Skeletal muscle atrophy	Likely pathogenic (class 2)	POMT2		c.1727dup	p.(Leu577Profs*8)	Het	Frameshift	Muscular dystrophy, limb-girdle 2N
12	M	Focal aware clonic seizure	Uncertain significance (class 3)	CHRNB2		c.1176C>A	p.(Asn392Lys)	Het	Missense	Nocturnal frontal lobe epilepsy-3 (ENFL3)
43	M	Dystonia; Bradykinesia; Tremor; Young-onset	Pathogenic (class 1)	PRKN	2	c.1321T>C	p.(Cys441Arg)	Het	Missense	Early-onset Parkinson disease, Autosomal recessive
35	F	Limb-girdle muscle atrophy; Proximal muscle weakness; Slowly progressive	Pathogenic (class 1)	DYSF		c.4551G>A	p.(Trp1517*)	Hom	Nonsense	Dysferlinopathy
65	F	Abnormal rapid eye movement sleep; Bradykinesia; Constipation; Dysarthria; Dysmetria; Hyposmia; Limb muscle weakness; Orthostatic hypotension; Resting tremor; Rigidity; Sleep disturbance; Tremor; Urinary retention	Uncertain significance (class 3)	ERBB4		<b>c.2936G&gt;A</b>	<b>p.(Arg979Gln)</b>	Het	Missense	Amyotrophic lateral sclerosis (ALS)

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
48	M	Abnormal nerve conduction velocity; Abnormal tongue morphology; Areflexia; Dysarthria; Dysphagia; EMG abnormality; EMG: chronic denervation signs; Erectile dysfunction; Fasciculations; Gynecomastia; Hyporeflexia; Jaw hyporeflexia; Limb muscle weakness; Lower limb muscle weakness; Proximal muscle weakness; Proximal muscle weakness in lower limbs; Proximal muscle weakness in upper limbs; Skeletal muscle atrophy; Tongue fasciculations; Upper limb amyotrophy; Upper limb muscle weakness	Uncertain significance (class 3) Uncertain significance (class 3)	KIF1A NEFH		c.2852T>C c.1048G>A	p.(Val951Ala) p.(Glu350Lys)	Het Het	Missense Missense	Spastic paraplegia-30 (SPG30); Autosomal recessive Amyotrophic lateral sclerosis; Autosomal recessive
45	F	Progressive proximal muscle weakness, hyporeflexia	Uncertain significance (class 3)	LDB3 RYR1		c.1804T>C c.9170T>C	p.(Tyr602His) p.(Phe3057Ser)	Het Het	Missense Missense	Myofibrillar myopathy-4 (MFM4); Autosomal dominant RYR1-related disorders: central core disease, mild congenital myopathy; Autosomal dominant/recessive

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**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygoty	Consequence	Molecular Diagnosis
24	F	Abnormality of the hallux; Areflexia; Biceps hyporeflexia; Brachioradialis hyporeflexia; Decreased patellar reflex; Decreased/absent ankle reflexes; Gowers sign; Hyporeflexia; Progressive proximal muscle weakness	Uncertain significance (class 3)	LDB3		<b>c.1804T&gt;C</b>	<b>p.(Tyr602His)</b>	Het	Missense	Myofibrillar myopathy-4 (MFM4); Autosomal dominant
66	M	Abnormality of somatosensory evoked potentials; Exercise-induced muscle stiffness; Hearing abnormality; Impaired proprioception; Impaired vibratory sensation; Kinetic tremor; Limb fasciculations; Neoplasm of the peripheral nervous system; Sensory ataxia; Tremor	Uncertain significance (class 3)	NF1		c.3497-12T>A	p.?	Het	Unknown	Neurofibromatosis type 1; Autosomal dominant

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
42	F	Abnormal gait; Abnormality of coordination; Abnormality of movement; Abnormality of voice; Ataxia; Brain imaging abnormality; Broad-based gait; Clumsiness; Difficulty descending stairs; Dysarthria; Dysdiadochokinesis; Dismetria; Functional motor deficit; Gait disturbance; Hot cross bun sign; Maternal diabetes; Poor fine motor coordination; Poor gross motor coordination; Postural instability; Speech articulation difficulties; Tip-toe gait; Vertigo; Weak voice	Likely pathogenic (class 2)	ATXN MYH7		c.2608C>T	heterozygous expanded allele (39 repeats) p.(Arg870Cys)	Het Het	Missense	Spinocerebellar ataxia type 2; Autosomal dominant Hereditary ventricular hypertrophy

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
38	M	Abnormality of the musculature of the lower limbs; Back pain; Distal lower limb muscle weakness; Distal muscle weakness; Foot dorsiflexor weakness; Gastrocnemius myalgia; Lower limb muscle weakness; Myopathy; Skeletal muscle atrophy; Tip-toe gait	Uncertain significance (class 3)	MYH7		c.2740C>T	p.(Gln914*)	Het	Nonsense	Myosin storage myopathy
11	M	Delayed gross motor development; Difficulty standing; Elevated circulating creatine kinase concentration; Falls; Hyporeflexia; Hypotonia; Muscle weakness; Muscular dystrophy; Myopathy; Pneumonia; Progressive muscle weakness; Proximal muscle weakness; Skeletal muscle atrophy	Pathogenic (class 1)	DMD	45	seq[GRCh37]del(chrX)(q21.1) chrX:g.(31964761_31986631)x0			Loss	X-linked inherited muscular dystrophies

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**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
16	M	Abnormal muscle tone; Abnormality of the shoulder girdle musculature; Difficulty climbing stairs; Difficulty descending stairs; Difficulty walking; Distal lower limb muscle weakness; Distal upper limb muscle weakness; Frequent falls; Functional motor deficit; Gait disturbance; Gowers sign; Hyporeflexia; Hypotonia; Limb muscle weakness; Limb-girdle muscle weakness; Lower limb amyotrophy; Lower limb muscle weakness; Muscle weakness; Myopathy; Proximal muscle weakness in lower limbs; Proximal muscle weakness in upper limbs; Skeletal muscle atrophy; Tip-toe gait; Upper limb amyotrophy; Upper limb muscle weakness; Waddling gait	Pathogenic (class 1)	SMN1						Spinal muscular atrophy (SMA); Autosomal recessive

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
20	M	Behavioral abnormality; Delayed speech and language development; Dialectic seizure; EEG abnormality; EEG with abnormally slow frequencies; EEG with central epileptiform discharges; EEG with focal epileptiform discharges; EEG with focal slow activity; EEG with frontal epileptiform discharges; EEG with temporal epileptiform discharges; Expressive language delay; Family history of cancer; Focal impaired awareness seizure; Impaired social interactions; Interictal epileptiform activity; Low voltage EEG; Motor stereotypy; Multifocal epileptiform discharges; Neurodevelopmental delay; Neurological speech impairment; Poor eye contact; Seizure precipitated by febrile infection; Tonic seizure	Uncertain significance (class 3) Uncertain significance (class 3)	SOX6 TRRAP			p.(Arg351Trp) p.(Asn980Lys)	Het Het	Missense Missense	Tolchin-Le Caignec syndrome; AD Developmental delay with or without dysmorphic facies and autism; AD

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygoty	Consequence	Molecular Diagnosis
19	M	Gradually progressive distal lower extremity weakness since 5 years of age, with foot drop on both lower extremities and atrophy of both calves	Pathogenic (class 1)	CPT2	4	c.585del	p.Pro196Leufs*51	Het		carnitine palmitoyltransferase II (CPTII or CPT2) deficiency; Autosomal recessive
34	M	Gradually progressive atrophy weakness and numbness of the left forearm, hand and fingers.	Pathogenic (class 1)	SCN4A	14	c.2614dup	p.Glu872Glyfs*7	Het		Autosomal dominant hypokalemic periodic paralysis type 2; hyperkalemic periodic paralysis; paramyotonia congenita; potassium-aggravated myotonia; autosomal recessive congenital myopathy; autosomal recessive congenital myasthenic syndrome

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**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygoty	Consequence	Molecular Diagnosis
49	M	Progressively worsening muscle atrophy, generalized weakness, tongue atrophy and fasciculations	Uncertain significance (class 3)	COL6A3	38	c.8168T>C	p.Ile2723Thr	Het	Autosomal dominant and recessive type VI collagenopathies	Autosomal dominant and recessive type VI collagenopathies
				FIG4	20	c.2250C>T	Silent	Het	Autosomal recessive Charcot-Marie-Tooth disease type 4J and Yunis-Varon syndrome	Autosomal recessive Charcot-Marie-Tooth disease type 4J and Yunis-Varon syndrome
				MYBPC3	15	c.1255C>T	p.Arg419Cys	Het	Autosomal dominant hypertrophic cardiomyopathy, dilated	Autosomal dominant hypertrophic cardiomyopathy, dilated
				MYOM1	4	c.473G>T	p.Arg158Ile	Het	cardiomyopathy and left ventricular noncompaction	cardiomyopathy and left ventricular noncompaction
				NEB	155	c.22609A>G	p.Lys7537Glu	Het	Autosomal dominant hypertrophic cardiomyopathy	Autosomal dominant hypertrophic cardiomyopathy
				PLEC	32	c.4790C>T	p.Ala1597Val	Het	Autosomal dominant hypertrophic cardiomyopathy	Autosomal dominant hypertrophic cardiomyopathy
				PRX	7	c.1869_1976del	p.Glu633_Pro668del	Het	Autosomal recessive nemaline myopathy 2	Autosomal recessive nemaline myopathy 2
				SYNE2	88	c.16246A>C	p.Met541Leu	Het	Autosomal recessive epidermolysis bullosa simplex with muscular dystrophy	Autosomal recessive epidermolysis bullosa simplex with muscular dystrophy
20	F	Dysphagia, muffled voice, atrophy of the trapezius muscle and tongue	Pathogenic (class 1)	FUS	Intron 14	c.1541+1G>A	Splice donor	Het	Autosomal dominant amyotrophic lateral sclerosis 6, with or without frontotemporal dementia	Autosomal dominant amyotrophic lateral sclerosis 6, with or without frontotemporal dementia

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**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
9	M	Proximal upper and lower extremity weakness, intellectual disability	Pathogenic (class 1)	DMD	45-50			Hem	Deletion	X-linked Duchenne muscular dystrophy
46	M	Right hand involuntary movements, right laterocollis and retrocollis	Uncertain significance (class 3)	TOR1A	5	c.769T>G	p.Leu257Val	Het		autosomal dominant dystonia 1
47	F	Involuntary movement of both lower extremities, with difficulty in ambulation	Pathogenic (class 1) Uncertain significance (class 3)	PINK1 LRRK2	5 51	c.1040T>C c.7570A>G	p.Leu347Pro p.Thr2524Ala	Hom Het		autosomal recessive early-onset Parkinson's disease 6 autosomal dominant Parkinson's disease 8
17	F	Progressive lower and upper extremity weakness, dysphagia	Pathogenic (class 1)	GNE	1	c.18T>A	p.Tyr6*	Hom		Autosomal recessive GNE-related myopathy and autosomal dominant sialuria
56	F	Right upper extremity weakness, tendency to fall backwards, involuntary movements, cervical and truncal dystonia	Uncertain significance (class 3) Uncertain significance (class 3) Uncertain significance (class 3)	ANO5 ANO5 CHKB COL6A1 NEB	19 19 9 5 49	c.2201T>C c.2209A>T c.980C>T c.642G>A c.6449C>T	p.Leu734Pro p.Met737Leu p.Ser327Phe Silent p.Ala2150Val	Het Het Het Het Het		Autosomal recessive limb-girdle muscular dystrophy type 2L, Miyoshi muscular dystrophy 3, autosomal dominant gnathodiaphyseal dysplasia Autosomal recessive congenital muscular dystrophy, megaconial type Autosomal dominant and recessive type VI collagenopathies Autosomal recessive nemaline myopathy 2, autosomal dominant nemaline myopathy

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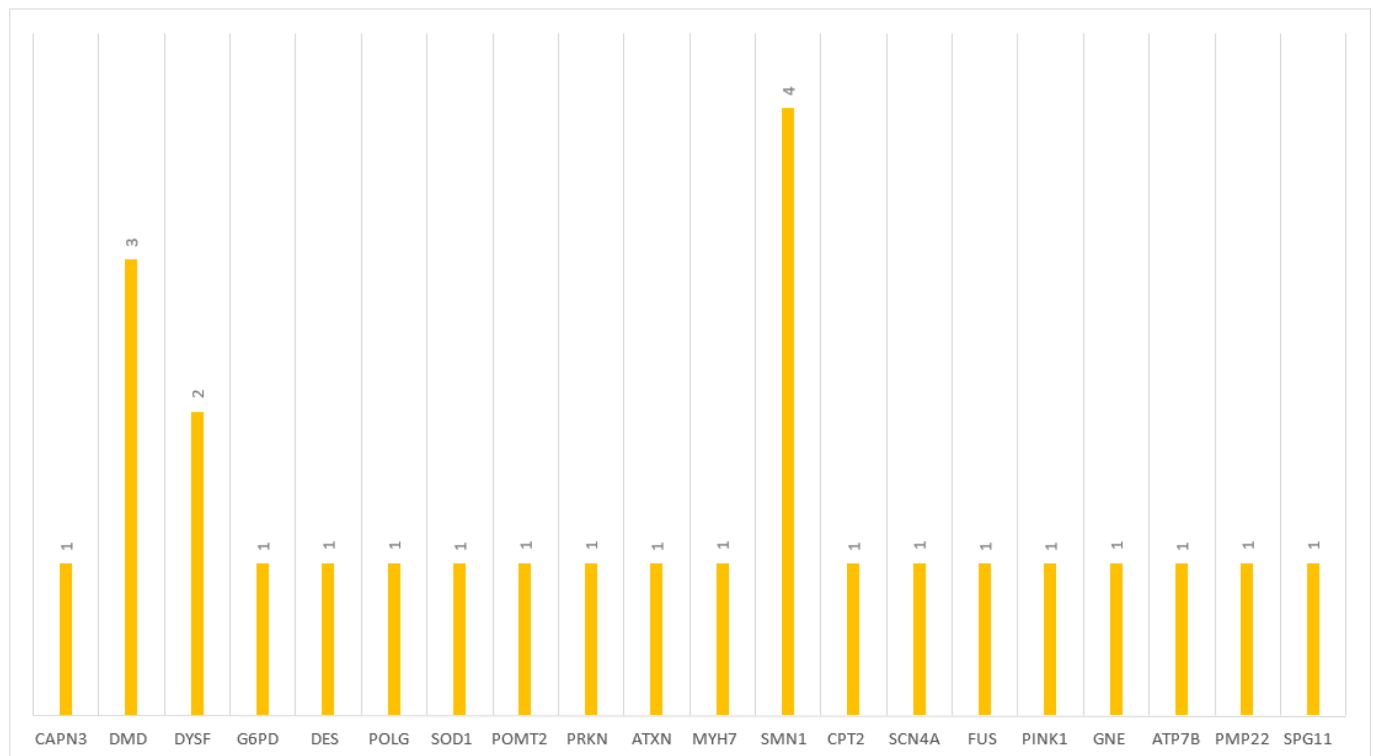
**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygosity	Consequence	Molecular Diagnosis
61	F	Left lower extremity weakness, gait disturbance, atrophy of both lower extremities, Tongue fasciculations	Uncertain significance (class 3)	GAA	5	c.913G>A	p.Gly305Arg	Het		Autosomal recessive Pompe disease (glycogen storage disease type II)
41	M	Clawing of left hand and foot	Pathogenic (class 1)	ATP7B	8	c.2333G>T	p.Arg778Leu	Het		Autosomal recessive Wilson disease
55	M	Pain and weakness of bilateral upper extremities, difficulty reaching things, dysphagia	Uncertain significance (class 3)	PLEC	32	c.4790C>T	p.Ala1597Val	Het		Autosomal recessive epidermolysis bullosa simplex with muscular dystrophy
30	M	Involuntary twitching and stiffening of neck	Uncertain significance (class 3)	ATP2A1 GFPT1 THAP1	15 3 3	c.1936G>A c.343G>C	p.Glu646Lys p.Ala115Pro	Het Het Het	Missense	Autosomal recessive Brody myopathy Autosomal recessive congenital myasthenic syndrome 12 Autosomal dominant torsion dystonia 6
65	M	Lower extremity weakness	Uncertain significance (class 3)	CIZ1	Intron 14	c.2295+6G>A	Intronic	Het		Autosomal dominant dystonia 23
63	F	Tremors of bilateral legs and hands	Uncertain significance (class 3)	TOR1AIP1		c.37G>A	p.Glu13Lys	Het		Autosomal recessive limb-girdle muscular dystrophy type 2Y
23	M		Pathogenic (class 1)	SMN1			(Entire coding sequence)	Het	Deletion	Autosomal recessive spinal muscular atrophy
33	F	Generalized dystonia	Pathogenic (class 1)	SMN1			(Entire coding sequence)	Het	Deletion	Autosomal recessive spinal muscular atrophy

(Continued)

**Table 1:** Summary of age, sex, phenotype, genotype, ACMG recommendation and molecular diagnosis of individuals with significant results (Continued)

Age	Sex	Phenotype (Expressed Traits)	Result/ACMG Recommendation	Gene	Exon	Nucleotide Change	Protein Change	Zygoty	Consequence	Molecular Diagnosis
2	M	Poor head control with minimal movement of extremities at 2 months of age	Pathogenic (class 1)	SMN1			(Entire coding sequence)	Het	Deletion	Autosomal recessive spinal muscular atrophy
43	M	Progressive weakness	Pathogenic (class 1) Pathogenic (class 1)	PMP22 SPG11		c.7105C>T	(Entire coding sequence) p.Gln2369*	Het Het	Gain	Autosomal dominant Charcot-Marie-Tooth disease type 1A Autosomal recessive hereditary spastic paraplegia 11



**Figure 2:** Identified genes associated with neuromuscular and movement disorders

assessment of diagnostic reliability. The diagnostic yield of NGS was 28.23% and VUS was 38.82%. Until this uncertainty can be resolved, precaution should be observed before utilizing the genetic test result to supply clinical management decisions. Among the confirmed genetic mutations presented, several rare diseases have been identified.

Current literature reveals a paucity of data regarding the genetic analysis of neuromuscular and movement disorders in underprivileged populations, which prompted the establishment of the International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) in June 2019, an initiative that is still ongoing. This center has conducted investigations connecting research facilities across India, Brazil, South Africa, Turkey, the United Kingdom, Zambia and the Netherlands. [5] Among the cohorts, the findings indicated that 18.1% of cases were identified as limb-girdle muscular dystrophy (LGMD), 15.5% as genetic peripheral neuropathies (PN), 9.4% as congenital myopathy or congenital muscular dystrophy (CM/CMD) and 8.6% as Duchenne muscular dystrophy or Becker muscular dystrophy (DMD/BMD), with other conditions accounting for less than 7%. The most frequently identified genes in solved probands

for congenital myopathies and muscular dystrophies included STAC3 (28 cases), RYR1 (8 cases) and COL6A2/3 (5 cases). For Duchenne and Becker muscular dystrophies, the predominant genes were DYSF (10 cases), CAPN3 (9 cases) and GNE (3 cases).[6]

Notably, the prevalence of different DMD variants exhibited significant variability between the Indian and South African cohorts. Among the 64 solved Indian participants, 60 (94%) presented with a deletion, three (5%) with a nonsense variant and one (1%) with a splice variant, with no Indian patients exhibiting a duplication. It is important to note that the population in this study comprised individuals of European, African and Asian descent. In contrast, our present study of the Filipino population identified DMD, DYSF and SMN1 as the most common genes yielding pathogenic results.[6]

A study conducted by Jogota, et al. identified several genetic movement disorders that are prevalent among Asian populations, including Wilson’s disease (WD), spinocerebellar ataxias (SCA) types 12, 31 and 36, Gerstmann-Sträussler-Scheinker disease (GSS), PLA2G6-related parkinsonism, adult-onset neuronal intranuclear inclusion disease (NIID), paroxysmal kinesigenic dyskinesia (PKD),

X-linked dystonia-parkinsonism (XDP), dentatorubral-pallidoluysian atrophy (DRPLA), Woodhouse-Sakati syndrome, benign adult familial myoclonic epilepsy (BAFME), Kufor-Rakeb disease and tremulous dystonia associated with variants of the calmodulin-binding transcription activator 2 (CAMTA2) gene. Similarly, our research has also identified individuals with Wilson's disease, spinocerebellar ataxia (SCA27), variant of young-onset Parkinson's disease (PARKN) and various dystonia disorders.[7]

Lastly, studies conducted in other Asian countries have reported higher diagnostic yields than ours. For instance, a study from India demonstrated a diagnostic yield of 87% for neuropathies and 49% for myopathies.[8,9] Similarly, data from China and Korea indicated 65% and 75% diagnostic yields, respectively, using NGS.[10,11] However, the spectrum of disorders identified in these studies, including Charcot Marie-Tooth disease, dysferlinopathy, GNE myopathy, DMD and LGMD is comparable to the findings in our research.

## CONCLUSION

To our knowledge, this is the first study to analyze a characterization of inherited neuromuscular and movement disorders in the Filipino population using NGS. Despite socioeconomic constraints in the country, there is an increasing awareness among Filipinos of the importance of genetic testing. The study yielded a diagnostic rate of 28% with comparable spectrum of hereditary neuromuscular and movement disorders to other Asian countries. However, the occurrence of VUS could be reduced through family segregation analyses and careful genotype-phenotype correlations. While these approaches are complex, particularly due to potential environmental interactions with the genotype, they are essential for achieving more precise interpretations.

This study underscores the importance of genetic testing and suggests that its maximization and enhanced availability could potentially lead to significant advancements in therapeutic management in the future for those with rare diseases, such as neuromuscular and movement disorders. Continued efforts in genetic research, particularly in Asia, are essential for enhancing the understanding of these conditions.

## LIMITATIONS

This study on neuromuscular and movement disorders among Filipinos is subject to several limitations. Firstly, the presented data with VUS should undergo further investigation into their pathogenic or benign nature. Doing so would require conducting family segregation analyses with in-depth genotype-phenotype correlations. This can be resource-intensive, and such analyses may not be financially feasible or accessible for the average Filipino family, limiting the ability to draw more definitive conclusions about the clinical significance of these variants.

Secondly, the study is constrained by a relatively small population size, as it only encompasses patients referred to the tertiary hospital in Manila by a specific physician. This referral bias may affect generalizability of the findings to the broader Filipino population, as it does not account for individuals with neuromuscular and movement disorders who may not have sought or received specialized care. Consequently, the results may not fully represent the spectrum of inherited neuromuscular and movement disorders within the entire Filipino demographic.

## ETHICAL CONSIDERATIONS

This study complies with the ethical principles set out in relevant guidelines, as specified in the Certificate of Agreement and Compliance in this research, and fully complies with the Philippine National Ethical Guidelines 2022 edition.

The principal investigator directly obtained informed consent using the Informed Consent form when conducting procedures at the Neuroscience Institute before the Neuromuscular Profiling/Genetic Testing procedure. This study is eligible for a waiver of informed consent under the guidelines set forth by the National Ethical Guidelines For Research Involving Human Participants (NEGRIHP), as it meets the criteria, which are: it poses no risk for physical, psychological, social, or economic harm to participants, and it involves only the description of cases, clinical profiles, courses of illness and genetic testing results. Moreover, this is purely observational and does not involve any interventions with patients. The study ensures the confidentiality and anonymity

of participants, thereby adhering to the ethical standards for waiver of consent.

The study is not company-sponsored or industry-funded. It is investigator-initiated and the subjects were patients of the co-author of this retrospective study. There are no conflicts of interest in this study. All of the patient's identity and personal data were not included in the study and identifiers were removed from the manuscript. The data will be accessed securely by the Principal Investigator and will be protected from illegal or inadvertent access by other people. It will also be stored for five years and will be deleted thereafter.

All data conveyed from this study will benefit future patients with the same clinical course and

presentation. The subjects have no direct benefit from this study.

#### **CONFLICT OF INTEREST**

In accordance with ethical standards and to maintain transparency in research, it is important to disclose that Dr. Raymond Rosales, the co-author of this study, is also the attending physician for all subjects involved in this research. Dr. Rosales has been treating these patients as outpatients between September 2018 and June 2024. This dual role of Dr. Rosales as both the treating physician and co-author may introduce potential conflicts of interest. To mitigate this, all data analysis and interpretation have been independently verified by other members of the research team who do not have direct clinical relationships with the patients.

## REFERENCES

- Lace B, Micule I, Kenina V, Setlere S, Strautmanis J, Kazaine I, et al. Overview of neuromuscular disorder molecular diagnostic experience for the population of Latvia. *Neurol Genet* [Internet]. 2022;8(3):e685. Available from: <http://dx.doi.org/10.1212/NXG.0000000000000685>
- Deenen JCW, Horlings CGC, Verschuuren JJGM, Verbeek ALM, van Engelen BGM. The epidemiology of neuromuscular disorders: A comprehensive overview of the literature. *J Neuromuscul Dis* [Internet]. 2015;2(1):73–85. Available from: <http://dx.doi.org/10.3233/jnd-140045>. PMID: 28198707.
- Woodcock IR, Fraser L, Norman P, Pysden K, Manning S, Childs A-M. The prevalence of neuromuscular disease in the paediatric population in Yorkshire, UK; variation by ethnicity and deprivation status. *Dev Med Child Neurol* [Internet]. 2016;58(8):877–83. Available from: <http://dx.doi.org/10.1111/dmcn.13096>
- Chung B, Wong V, Ip P. Prevalence of neuromuscular diseases in Chinese children: a study in southern China. *J Child Neurol* [Internet]. 2003;18(3):217–9. Available from: <http://dx.doi.org/10.1177/08830738030180030201>. PMID: 12731646.
- Pajo AT, Espiritu AI, Jamora RDG. Scientific impact of movement disorders research from Southeast Asia: A bibliometric analysis. *Parkinsonism Relat Disord* [Internet]. 2020;81:205–12. Available from: <http://dx.doi.org/10.1016/j.parkreldis.2020.10.043>
- Wilson LA, Macken WL, Perry LD, Record CJ, Schon KR, Frezatti RSS, et al. Neuromuscular disease genetics in under-represented populations: increasing data diversity. *Brain* [Internet]. 2023;146(12):5098–109. Available from: <http://dx.doi.org/10.1093/brain/awad254>
- Jagota P, Lim S-Y, Pal PK, Lee J-Y, Kukkle PL, Fujioka S, et al. Genetic movement disorders commonly seen in Asians. *Mov Disord Clin Pract* [Internet]. 2023;10(6):878–95. Available from: <http://dx.doi.org/10.1002/mdc3.13737>. PMID: 37332644; PMCID: PMC10272919.
- Chakravorty S, Nallamilli BRR, Khadilkar SV, Singla MB, Bhutada A, Dastur R, et al. Clinical and genomic evaluation of 207 genetic myopathies in the Indian subcontinent. *Front Neurol* [Internet]. 2020;11(559327):559327. Available from: <http://dx.doi.org/10.3389/fneur.2020.559327>
- Sharma S, Govindaraj P, Chickabasaviah YT, Siram R, Shrotri A, Seshagiri DV, et al. Genetic spectrum of inherited neuropathies in India. *Ann Indian Acad Neurol* [Internet]. 2022;25(3):407–16. Available from: [http://dx.doi.org/10.4103/aian.aian\\_269\\_22](http://dx.doi.org/10.4103/aian.aian_269_22)
- Dai Y, Wei X, Zhao Y, Ren H, Lan Z, Yang Y, et al. A comprehensive genetic diagnosis of Chinese muscular dystrophy and congenital myopathy patients by targeted next-generation sequencing. *Neuromuscul Disord* [Internet]. 2015;25(8):617–24. Available from: <http://dx.doi.org/10.1016/j.nmd.2015.03.002>
- Seong M-W, Cho A, Park HW, Seo SH, Lim BC, Seol D, et al. Clinical applications of next-generation sequencing-based gene panel in patients with muscular dystrophy: Korean experience: Clinical applications of NGS in muscular dystrophy. *Clin Genet* [Internet]. 2015;89(4):484–8. Available from: <http://dx.doi.org/10.1111/cge.12621>



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