Supplementary Table 1: Detailed phenotypical and genetic features of paediatric-onset motor neuronopathies.

	GEMIN5 *Kour et al, 2021*[1]	***EXOSC9*** *Burns et al, 2018*[2] *Bizzari et al, 2019*[3] *Sakamoto et al, 2021*[4] *Dabaj et al, 2022*[5]	***RBM7*** *Giunta et al, 2016*[6]	***TRIP4*** *Knierim et al, 2016*[7] *Töpf et al, 2021*[8]	***ASCC1*** *Knierim et al, 2016*[7] *Giuffrida et al, 2020*[9] *Lu et al, 2020*[10] *Rosano et al, 2021*[11]	***ADPRHL2*** *Beijer et al 2021*[12]	***NRCAM*** *Kurolap et al, 2022*[13] *Elahi et al, 2023*[14]	***MME*** *Hong et al, 2019*[15]	***UBE3C*** *Gopinath et al, 2007*[16]	***SLC5A6*** *Holling et al, 2022*[17]	***SLC25A21*** *Boczonadi et al, 2018*[18]	***BANF1*** *Marcelot et al, 2023*[19]	***NAGLU*** *Lopergolo et al, 2023*[20]
Number of cases	>10 from different families	10 from different families	1	6 from 4 families[c]	5 from 4 families[c]	3[a, b]	2[b]	1[a]	9 from single family	5 from 3 families	1	1	1
Age at onset of neuropathy symptoms	Birth – 1st decade	Birth – 3 years	1 month	Birth	Birth	2nd decade[a]	2nd decade	16 years[a]	3 – 40 years	1st – 2nd decade	3 years	3 years	2 years and 6 months
Initial symptoms	Develop-mental delay ± hypotonia	Develop-mental delay ± hypotonia	Hypotonia, poor sucking, failure to thrive	Arthro-gryposis multiplex congenita, congenital fractures and neonatal respiratory distress	Arthro-gryposis multiplex congenita, congenital fractures and neonatal respiratory distress	Walking instability, ± fatigue ± atrophy of intrinsic hand muscles distal lower limbs	Distal lower limb weakness	Lower limb weakness	Walking and running difficulties due to lower limb weakness	Fine motor difficulties ± slow walking	Deterior-ated walking, frequent falls	Abnormal and clumsy gait	Weakness in upper and lower limbs
Muscle strength	Generalized weakness	Proximal and distal weakness (1 year)	Generalized weakness	Generalized weakness, hypotonia	Generalized weakness, hypotonia	Distal pre-dominant generalized weakness	Distal or distal-pre-dominant weakness	Distal and lower extremity pre-dominant weakness (24 years)	Distal (pre-dominantly in upper extremities) or generalized weakness	Weakness and atrophy in hands, foot drop, proximal muscles are normal (19 years)	Distal weakness	Diffuse muscle weakness that affected legs more than arms, a complete foot drop (8 years)	Widespread weakness, Atrophy of distal parts of extremities (60 years)
Pyramidal signs	Hyperreflexia	-	-	-	-	± (spasticity)	-	-	Rarely (Brisk reflexes, Babinski sign)	Brisk reflexes, Achilles clonus	Brisk reflexes, Achilles clonus	-	-
Sensory signs	NA	-	-	NA	NA	Hypo-esthesia in tip toes, diminished position, and vibration	-	-	-	-	-	Slightly decreased cold sensation of toes	Paresthesia, thermal and painful hypo-esthesia in limbs

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						sense in lower legs and hands							
Additional neurological features	Tremor ± ID ± head nodding ± ataxia ± epilepsy ± micro-cephaly ± respiratory distress ± oculomotor apraxia	Seizures ± psycho-motor regression ± tongue fasciculation ± respiratory insufficiency ± nystagmus	Respiratory difficulties	May result in stillbirth	May result in stillbirth	ID ± seizures ± nystagmus ± postural tremor ± restrictive pulmonary function	-	Postural tremor	-	Tremor ± cerebellar signs	Mild facial weakness, tongue fascic-ulations, decreased FVC	Swallowing and respiratory difficulties	-
Skeletal deformities	CMA ± claw hands	CMA ± joint contract-ures ± valgus deformities	-	CMA ± multiple fractures	CMA ± multiple fractures ± talipes equinovarus ± joint contract-ures	Pes cavus ± scoliosis	Pes cavus ± hammer toes ± scoliosis ± hyper-lordosis ± claw hands	Pes cavus ± joint contract-ures	Pes cavus ± hammer toes	-	Claw hands, scoliosis	Scoliosis	-
Systemic features	High-arched narrow palate	Facial dysmorfism ± short stature ± bone fractures ± micro-cephalia ± failure to thrive ± strabismus ± esotropia	Cachexia	Pleural effusion and chylothorax, biliary calculi and soft tissue emphysema	Tent-shaped mouth, micro-retro-gnathia, polyhydro-amniosis, cardio-myopathy, reduced prenatal movements	Growth retardation ± left ventricle hypertrophy ± mitral insufficiency ± micro-gnathia ± hyper-hidrosis ± absent trunk hair	Cataracts	-	-	Dilated cardio-myopathy ± inguinal hernia	Failure to thrive	Poor weight gain	-

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Disease course	Static or progressive course	Progressive (3 patients died during the follow-up between 1.5 and 10 years)	Progressive (Died due to respiratory decompens-ation)	Progressive (lethal in first 2 years), later onset myopathy cases are described	Progressive (lethal in first 2 years), later onset myopathy cases are described	Progressive	NA	NA	NA	Progressive	Progressive course, unable to stand at 18 years	Progressive (Wheelchair use at 10 years)	Slowly progressive
EMG / Nerve conduction studies	Severe neurogenic pattern, motor neuropathy ± SN ± myopathic pattern	Motor neuron-opathy	Low CMAPs with chronic early and late re-innervation	NA	NA	Axonal motor poly-neuropathy ± mild SN	Segmental neurogenic involvement in L1-S2 and C8-D1, and myopathic motor unit potentials ± SN	Length-dependent motor neuropathy	Slowed tibial conduction in the older patients (range 37–50 m/s) with normal CMAPs	Motor neuropathy ± neuron-opathy ±, mixed demyelin-ating and axonal neuropathy	Severe neurogenic changes	Neurogenic process with diffuse fibrillations and reduced motor responses	Bilateral chronic motor denervation on C7-T1 myotomes
Cranial MRI	Cerebellar or ponto-cerebellar atrophy ± white matter changes	Cerebellar atrophy ± cerebral atrophy ± white matter atrophy	Normal	Hypoplastic cerebellum, necrosis, haem-orrhage of occipital cortex	Abnormal cortical gyration, lateral ventricle dilatation, simplified gyral pattern of the frontal lobes and enlargement of the external CSF spaces	Normal or mild white matter hyper-intensity lesions	Normal or arachnoid cyst of the posterior fossa	NA	Normal	NA	Normal	NA	NA
Nerve biopsy	NA	NA	NA	Normal myelin-ization but with loss of unmyelinate	NA	NA	NA	NA	Chronic axonal neuropathy	Normal	Axonopathy with mild and patchy loss of	NA	NA

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				d axons as documented by "empty" pouches							myelinated fibres		
Other investigations	Abnormal EEG	Pronounced streak-like and mixed increase in echogenicity with widespread evidence of active fasciculations in muscle ultrasound Denervation signs in muscle biopsy, normal EEG	Fibre type grouping of small and hypertrophic fibres in muscle biopsy	Reduced fiber size, increased fiber-size variation, clustered type I fibers, atrophy in muscle biopsy	Fiber size variation and atrophy, type I fiber grouping, oxidative rims, type I fiber predominance in muscle biopsies	Intermittent bifrontal theta waves ± frontocentral sporadic epileptiform activity in EEG	Elevated creatine kinase	NA	-	Low serum biotin, muscle biopsy showed neurogenic pattern	Microcytic anemia, lactic aciduria, increased urinary 3-hydroxyisovaleric and glutaric acids, Marginally increased CSF lactate	NA	20% reduced urinary alpha-N-acetylglucosaminidase activity
Overlapping disorder	PCH	PCD1D	-	Congenital myopathy	Congenital myopathy	CONSDIAS, PAMP Syndrome	NDD with neuromuscular and skeletal abnormalities	CMT2T, SCA43?	NDD with absent speech and movement and behavioral abnormalities	SMVTD	-	Nestor-Guillermo progeria syndrome	CMT2V, MPS3B
Zygosity and variants with motor neuronopathy phenotype	Hom H923P, Hom H913R, Hom D704E,	Hom L14P, CH L14P and R161*, CH L80R and R162Lfs*3	Hom P79R	Hom, R254*, Hom R278*, CH R254* and R278*	Hom E53Gfs19*, CH S311* and deletion of exon 5, CH R343* and 10q22.1	Hom V335G, Hom G77T	Hom S134P, Hom Q25*	CH V440_K472 del and, P676L	CSV	Hom S429G, CH R94* and Y162C	Hom L232R	Het G16R	Het A479T

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	Hom G683D, Hom S1000P, CH I988F and L1367P, CH I988F and S1311Lfs*7, CH H162R and L1367P	Hom G51R, CH L14P and R212*			micro-deletion, CH Arg156* and c.297-8 T>G								

Abbreviations: CH: Compound heterozygous; CMA: Congenital multiplex arthrogryposis; CMAP: Compound muscle action potential; CMT: Charcot Marie Tooth disease; CONSDIAS: Stress-induced childhood-onset neurodegeneration with variable ataxia and seizures syndrome; CSF: Cerebrospinal fluid; CSV: Complex structural variant**;** EEG: Electroencephalography; EMG: Electromyography; FVC: Forced vital capacity; Het: Heterozygous; Hom: Homozygous; ID: Intellectual disability; MPS: Mucopolysaccharidosis; MRI: Magnetic resonance imaging; NA: Not applicable; NDD: Neurodevelopmental disorder; PAMP: Episodic psychosis, ataxia, motor neuropathy with pyramidal signs; PCH: Pontocerebellar hypoplasia; SCA: Spinocerebellar ataxia; SN: Sensory neuropathy; SMVTD: Sodium-dependent multivitamin transporter deficiency

[a]: Later-onset cases are excluded

[b]: Cases with neuropathy as a part of complex disease spectrum are excluded

[c]: Cases described as congenital myopathy are exluded

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