SUPPLEMENTARY MATERIAL

Supplemental Table 1. SMA, SMA-like phenotype and conditions in which neurogenic EMG changes are found in the context of a complex disorder

Gene	Inheritance	Salient or peculiar features	Age of onset	Disease
SMA with severe congenital phenotype				
SMN1	AR	Bell-shaped thorax and diaphragmatic breathing	Birth - first months	SMA type 0-1
UBE1	X-linked	Proximal weakness, proximal and finger contractures, respiratory insufficiency, dysmorphic features, myopathic facies. Death in less than 2 years of age	Birth or infancy	X-linked infantile SMA type 2
SCO2	AR	Like SMA type 1 with dilated cardiomyopathy, ptosis, impaired extraocular movements	Infantile	SMA phenotype due to mitochondrial dysfunction
IGHMBP2	AR	Severe distal weakness. Diaphragmatic paralysis with sparing of intercostal muscles. Death or respiratory failure in less than 3 months. Occasionally, mild contractures of the knee and ankle.	Birth-2 months	SMARD1
LAS1L	X-Linked R	Distal weakness at birth and early respiratory failure. Tongue fasciculations. Mild contractures of fingers and toes	Birth	SMARD2
RBM7	AR	Cachexia, diffuse weakness, early respiratory impairment. No fasciculations. Tendon reflexes: Reduced	12 months	Spinal motor neuropathy
SMA + CNS manifestations				
VRK1	AR	Hypotonia, weakness, distal symmetric polyneuropathy, ataxia, nystagmus, contractures, microcephaly. Typical MRI findings.	Congenital to 6 months	SMA with pontocerebellar hypoplasia type 1 (PCH 1)
RARS2	AR	Delayed development, problems with movement, and intellectual disability. Typical MRI findings.	1st year	PCH 1
EXOSC8	AR	Spinal motor neuron disease + Typical MRI findings.	Congenital	PCH 1C
EXOSC3	AR	Progressive microcephaly, distal contractures, oculomotor apraxia. Respiratory involvement. Typical MRI findings.	Congenital	PCH 2
TSEN54	AR	Severity depends on the form. Severe developmental delay. Spasticity, extrapyramidal signs (e.g. choreoathetosis, dystonic attacks), **seizures**. Feeding difficulties, respiratory impairment. Typical MRI findings.	Birth-1st year	PCH 2-4-5
AGTPBP1	AR	Early onset cerebellar atrophy, developmental arrest with progressive muscle weakness, and feeding and respiratory difficulties	1st year	Neurodegeneration, childhood-onset, with cerebellar atrophy
TBCE	AR	Hypotonia, developmental delay. Absent speech or dysarthria. Moderate to severe cognitive impairment. Distal weakness and wasting. Spastic tetraparesis. Ataxia (60%), optic atrophy (40%), scoliosis. Course: Progressive	Birth- 14 months	Encephalopathy, progressive, with amyotrophy and optic atrophy
TBCD	AR	Developmental delay.. Proximal > Distal weakness. Respiratory involvement. Tongue fasciculations, microcephaly **seizures**, optic atrophy	Congenital	Encephalopathy, progressive, early-onset, with brain atrophy and thin corpus callosum
TBCK	AR	Hypotonia, severe psychomotor delay, feeding difficulties, progressive respiratory impairment, distinctive facial features	Birth-infancy	Hypotonia, infantile, with psychomotor retardation and characteristic facies
SPTBN4	AR	Congenital hypotonia, profound weakness with areflexia, respiratory and feeding difficulties, and profound developmental delay with no language development. **Seizures**, cortical visual impairment and deafness. Can be associated with axonal or mixed sensory motor neuropathy.	Birth	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness
PLA2G6	AR	Neurocognitive regression, combination of pyramidal, extrapyramidal, and peripheral signs. Optic atrophy, nystagmus. Brain MRI: cerebellar atrophy, claval hypertrophy, iron in GP and SN.	6mo-3years	Neurodegeneration with brain iron accumulation-2A
AIFM1	X-linked	SMA-like hypotonia and proximal weakness. Continuous involuntary movements in the hands and feet. Tongue fasciculations, muscle wasting. Absent DTR. **Seizures**. Neuro developmental delay. Progressive respiratory and feeding difficulties. Brain MRI: frontotemporal atrophy with a lactate peak	Birth- first months	Combined oxidative phosphorylation deficiency, Also causes CMT4X

		at spectroscopy. High Lactate & Pyruvate in serum & CSF. Treatment with riboflavin!		
+	**Predominant movement disorder/ dystonia**			
SCP2	AR	Dystonia, Hypergonadotropic hypogonadism, Azoospermia, Saccadic eye movements, Brisk reflexes in arms, diminished in legs, Intention tremor, ataxia, Hyposmia. MRI brain: hyperintensities in thalamus, "butterfly-like" lesions in pons, lesions in occipital regions	Childhood to Teens	Leukoencephalopathy with dystonia and motor neuropathy
HEXA	AR	TSD: early onset, severe progressive. Blindness, 'cherry-red' spot on fundus examination. Usually fatal by the age of 2-3 years. Juvenile: Muscle atrophy, muscle cramping, fasciculations, proximal greater than distal weakness. Ataxia, dystonia, dysarthria. MRI brain: cerebellar atrophy. EMG/NCS: axonal sensorimotor polyneuropathy.	Infancy to late teens - Early adulthood	Tay-Sachs disease (TSD), Juvenile GM2-gangliosidosis
C19orf12	AR	Dysarthria, Spasticity, Dystonia, parkinsonism, progressive distal great than proximal weakness, optic atrophy, slow saccades, cognitive decline, psychiatric manifestations	3-39 years	
+	**Predominant spasticity/upper motor neuron**			
SPTLC1	AD	Spasticity followed by diffuse lower motor neurons involvement, tongue fasciculation, scoliosis, respiratory involvement	Early-childhood to early adulthood	Juvenile ALS
SPTLC2	De novo/AD	Spasticity followed by diffuse lower motor neurons involvement, tongue fasciculation, dysphagia,, respiratory involvement	Neonatal to early childhood	Juvenile ALS
HNRNPA1	AD	Variable phenotype, from Juvenile ALS to HMN and distal myopathy		Juvenile ALS, HMN
+	**Seizures**			
ASAH1	AR	SMA-like with proximal weakness first in legs and then in arms. Later respiratory failure occurs	3-5 years	SMA with myoclonic epilepsy
+	**Early bulbar involvement**			
SLC52A2 and *SLC52A3*	AR, rarely AD	Progressive pontobulbar palsy, sensorineural hearing loss, axial and distal muscle weakness, optic atrophy, ataxia caused by sensory neuropathy, respiratory involvement. Beneficial treatment with high-dose riboflavin (10 mg/kg per day)	Infancy -3rd decade	Brown-Vialetto-Van-Laere syndrome (BVVL) -Riboflavin Transporter Disorders (RTD)
SLC52A2 and *SLC52A3*	AR or AD	Progressive pontobulbar palsy, axial and distal muscle weakness, optic atrophy, ataxia caused by sensory neuropathy, respiratory involvement. **No** hearing loss. Beneficial treatment with high-dose riboflavin (10 mg/kg per day)	Childhood	Fazio-Londe syndrome - Riboflavin Transporter Disorders (RTD)
UBQLN1?	AR	Bulbar weakness Vocal cord paralysis ± sensorineural hearing loss	Juvenile	Madras pattern Motor Neuron Disease (MMND)
UBQLN2	AR	Progressive pontobulbar palsy + respiratory failure and upper motor neuron signs	Early adulthood	Madras pattern Motor Neuron Disease (MMND)

Supplementary Table 2. Summary of main early-onset neuronopathies

Gene symbol	OMIM ref	Inheritance	Protein/Function	Salient or peculiar features	Age of onset	Associated conditions
Conditions with predominant distal involvement						
HSPB1	608634	AD/AR	UPR; stabilization of microtubules?	*Clinical*: lower limb predominance, slowly progressive, DTR absent or brisk. Neurophysiology: diffusively reduced CMAPS	Early adulthood, rarely in the 1st decade (median 30y, range 4-66)	HMN2B, CMT2F
HSPB8	158590	AD	UPR	*Clinical*: Possible onset with talipes + hip dislocation and delayed motor milestones. UL predominance possible. DTR brisk	Congenital to Adulthood	HMN2A, CMT2L
HSPB3	613376	AD	-	*Clinical*: Asymmetric distal weakness	3rd decade	HMN2C, CMT2
ATP7A	300489	X-linked	Copper transport	*Clinical*: Distal-onset wasting and weakness. Early weakness of legs with slow progression; remain ambulatory. Pes cavus	2-61y	X-linked HMN (SMAX3)
WARS	617721	AD	tryptophanyl-tRNA synthetase	*Clinical*: Slowly progressive distal weakness and atrophy in the feet, legs and hands	Juvenile onset (9-13y)	HMN9
FBXO38	615575	AD	Transcriptional activator	*Clinical*: Calf-predominance	13-48y	HMN2D
DNAJB2	614881	AR	Cochaperone	*Clinical*: progressive distal weakness LL. Milder and later proximal LL weakness. UL mildly affected or spared	16-23y	DSMA5
HINT1	137200	AR	Purine phosphoramidase	*Clinical*: Distal weakness and atrophy LL and UL ± sensory involvement and neuromyotonia (absent in 20% of cases)	1st decade	HMN with neuromyotonia
IGHMBP2	604320	AR	Helicase	*Clinical*: Either classic SMARD phenotype or milder cases with delayed motor milestones, distal weakness and only later (end of 1st decade) respiratory involvement	Congenital to early childhood	HMN6/SMARD, CMT2S
GARS	600794	AD	Aminoacyl-tRNA synthetases. Disruption of the VEGF/Nrp1 signalling pathway?	*Clinical*: - 2nd decade onset, upper-limb predominance, - <2 y onset forms with LL>UL involvement, - Congenital onset SMARD-like with respiratory impairment, vocal cord palsy	5-20 years, Congenital	CMT2D, HMN5A, SMARD like phenotype
REEP1	614751	AD	ER-mitochondrial interactions	*Clinical*: Preferential hand involvement (split sign) but also distal LL involvement and pes cavus	1st-2nd decade	HMN5B, HSP31
BSCL2	619112	AD	UPR	*Clinical*: Weak hands (thenar greater than first dorsal interosseous), Foot deformities, Peroneal weakness, brisk DTRs	Juvenile onset (median 15 y, range 4-40)	HMN5C, Silver syndrome
TRPV4	600175, 181405	AD	Ion Channel – Possible disruption of mitochondrial axonal trafficking	*Clinical*: talipes equinovarus, vocal cord palsy, progressive scoliosis; Respiratory involvement, hearing loss, and skeletal dysplasia present in <25%. MRI muscle:	Congenital to childhood	HMN7, CMT2C, SPSMA, AMC, skeletal dysplasia

				preservation of biceps femoris and medial gastrocnemius		
SLC5A7	158580	AD	Pre-synaptic choline transporter	*Clinical:* hand weakness and wasting (split-hand) and subsequent distal leg weakness. Vocal-cord paralysis	11-16 y	HMN7A, CMS 20
DCTN1	607641	AD	Axonal transport along the microtubules	*Clinical*: either vocal cord paralysis, facial and distal UL and LL weakness. Also, Congenital onset (talipes) slowly progressive. *Brisk reflexes	From congenital to Early adulthood	HMN7B, Juvenile ALS, Perry Syndrome
SIGMAR1	605726	AR	ER Chaperone	*Clinical*: Distal weakness and atrophy, LL first, then UL. Brisk DTR.	1st decade (6-12y)	DSMA2, Juvenile ALS
SETX	606002, 602433	AR, AD	RNA and DNA helicase	*Clinical*: HMN + Pyramidal signs	Juvenile	HMN + pyramidal
AAAS	231550	AR	Nuclear protein import	*Clinical:* the typical triad of achalasia, alacrimia and adrenal insufficiency variably associated with motor neuronopathy	1st decade (1-10y)	Triple A syndrome
SORD	618912	AR	Oxidation of sorbitol to fructose	*Clinical:* distal weakness and atrophy, slowly progressive. Sensory involvement common	Juvenile onset (rarely <10y)	N/A
MFN2	n/a	AD	Mitochondrial fusion	*Clinical*: might be associated with a phenotype similar to early onset HMN with predominant motor LL involvement (distal)	1st decade	CMT2A
SMA-LED or neuronopathies with early proximal weakness						
DYNC1H1	58600	AD	Axonal retrograde transport + other housekeeping functions	*Clinical:* proximal ≥distal LL weakness. Cognitive impairment, ADHD in ~1/3 of cases, MRI: Muscle involvement is peculiar (see text), CNS: polymicrogyria in >20% of cases	Congenital to adulthood	SMALED 1, HMN1, AMC, ID + MCD
BICD2	615290, 618291	AD	Cargo adaptor protein, interact with dynein/kinesin complex. Localize Rab6 to Golgi	*Clinical:* phenotype usually similar to SMALED1, Respiratory involvement in up to 30%, MRI: brain abnormalities reported only in de novo cases	Congenital to adulthood	SMALED2A, SMALED2B, AMC
SYT2	616040	AD	Ca^{++} sensors for vesicular trafficking and exocytosis	*Clinical*: slowly progressive predominantly motor neuropathy, Cooccurrence of presynaptic NMJ dysfunction and LMN defect	Childhood (second half of 1st decade) to adulthood	Pre-synaptic CMS (AR)
PLEKHG5	611067	AR	Nuclear factor kappa-B activator	*Clinical*: SMA3a like phenotype, progressive respiratory impairment	Childhood (2 - 11 years)	CMT-RIC
VWA1	619216	AR	ECM component	*Clinical:* congenital **or** early onset feet deformities. Distal weakness (atrophy not common). Proximal weakness can be observed. Patellar and hip dislocation, MRI: peculiar pattern (see text), EMG and Muscle biopsy: mixed neurogenic/myopathic changes	2 years-adulthood	N/A

Supplemental Table 3. Genes associated with neurogenic arthrogryposis

Gene	Inheritance	Protein/Function	Salient or peculiar features	Disease
DYNC1H1	AD	Axonal retrograde transport + other housekeeping functions		SMALED 1, HMN1, AMC, ID + MCD
BICD2	AD	Cargo adaptor protein, interact with dynein/kinesin complex. Localize Rab6 to Golgi		SMALED2A, SMALED2B, AMC
TRPV4	AD	Ion Channel – Possible disruption of mitochondrial axonal trafficking		HMN7, CMT2C, SPSMA, AMC, skeletal dysplasia
ECEL1	AR	Zinc metalloproteases	Distal arthrogryposis, ulnar deviation, respiratory impairment in some patients	Arthrogryposis, Distal, Type 5d
UBE1	X-linked	Ubiquitin activating enzyme	Pattern of weakness similar to classic SMA, Proximal and finger contractures. Myopathic facies, Respiratory insufficiency, Dysmorphic features Death < 2 years of age	SMAX2
GLE1	AR	Nuclear trafficking and gene expression regulator	Severe phenotype with respiratory and bulbar impairment + pyramidal and extrapyramidal signs and premature death. 3 patients reported with "milder" phenotype	Lethal congenital contracture syndrome 1
ERBB3	AR	Epidermal growth factor receptor tyrosine kinase	AMC + gut dysmotility	Autosomal recessive familial visceral neuropathy 1
ERGIC1	AR	Transport between ER and Golgi	Neurogenic AMC (flexion elbows and kness + equinovarus). Not evolving	
SMN1	AR	Housekeeping	Severe forms of SMA	SMA type 0