

# Adult-onset non-5q proximal spinal muscular atrophy: a comprehensive review

Atrofia muscular espinhal não-5q proximal de início no adulto: uma revisão abrangente

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## ABSTRACT

**Background:** Adult-onset spinal muscular atrophy (SMA) represents an expanding group of inherited neurodegenerative disorders in clinical practice. **Objective:** This review aims to synthesize the main clinical, genetic, radiological, biochemical, and neurophysiological aspects related to the classical and recently described forms of proximal SMA. **Methods:** The authors performed a non-systematic critical review summarizing adult-onset proximal SMA presentations. **Results:** Previously limited to cases of *SMN1*-related SMA type 4 (adult form), this group has now more than 15 different clinical conditions that have in common the symmetrical and progressive compromise of lower motor neurons starting in adulthood or elderly stage. New clinical and genetic subtypes of adult-onset proximal SMA have been recognized and are currently target of wide neuroradiological, pathological, and genetic studies. **Conclusions:** This new complex group of rare disorders typically present with lower motor neuron disease in association with other neurological or systemic signs of impairment, which are relatively specific and typical for each genetic subtype.

**Keywords:** Muscular Atrophy, Spinal; Neurodegenerative Diseases; Motor Neuron Disease; Neuromuscular Diseases.

## RESUMO

**Antecedentes:** Atrofia muscular espinhal (AME) de início no adulto representa um grupo de doenças neurodegenerativas hereditárias em expansão na prática clínica. **Objetivo:** Este artigo de revisão sintetiza os principais aspectos clínicos, genéticos, radiológicos, bioquímicos e neurofisiológicos relacionados às formas clássicas e recentemente descritas de AME proximal do adulto. **Métodos:** Os autores realizaram uma revisão crítica não sistemática descrevendo as principais apresentações de AME proximal de início no adulto. **Resultados:** Previamente restrito às apresentações de AME tipo 4 associada ao gene *SMN1*, este grupo atualmente envolve mais de 15 diferentes condições clínicas que compartilham entre si a presença de comprometimento progressivo e simétrico do neurônio motor inferior se iniciando no adulto ou no idoso. Novos subtipos clínicos e genéticos de AME proximal de início no adulto foram reconhecidas e são alvo atuais de estudos direcionados a aspectos neuroradiológicos, patológicos e genéticos. **Conclusões:** Este novo grupo complexo de doenças raras tipicamente se apresenta com doença do neurônio motor inferior em associação com outros sinais de comprometimento neurológico ou sistêmico, os quais apresentam padrões relativamente específicos para cada subtipo genético.

**Palavras-chave:** Atrofia Muscular Espinhal; Doenças Neurodegenerativas; Doença dos Neurônios Motores; Doenças Neuromusculares.

## INTRODUCTION

Motor neuron disease (MND) represents a wide and expanding group of different neurological disorders resulting from isolated or combined involvement of lower and upper

motor neurons. The main adult-onset clinical disorder in this group is amyotrophic lateral sclerosis (ALS)<sup>1</sup>, however there is a high number of sporadic and hereditary neurological diseases that may present with MND phenotype and should be considered in the differential diagnosis (Table 1)<sup>2,3,4</sup>.

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**Table 1. Classification of primary adult- and childhood-onset motor neuron disease<sup>1,2,3,4,7</sup>.**

Classification of Motor Neuron Disease (MND) group*
Upper and lower MND
Amyotrophic Lateral Sclerosis (ALS) (sporadic, familial; juvenile) Mills' syndrome (progressive hemiplegic variant)**
Upper MND
Primary Lateral Sclerosis (PLS) (sporadic, familial)
Lower MND
Progressive Muscular Atrophy (Duchenne-Aran syndrome) (sporadic) SMN1-associated (5q) Spinal Muscular Atrophy (SMA) (hereditary) Non-5q (non-SMN1/SMN2) SMA (familial, hereditary) Distal SMA (distal hereditary motor neuropathy) Proximal non-5q SMA "Flail-arm" syndrome (Vulpien-Bernhardt) (sporadic, familial) O'Sullivan-McLeod syndrome (sporadic) Hirayama disease (Juvenile monomelic distal amyotrophy) (sporadic) "Flail-leg" syndrome (pseudopolyneuritic form) (sporadic)
MND with marked bulbar and cranial nerve involvement
Progressive Bulbar Palsy (sporadic) Kennedy's disease (X-linked spinal and bulbar muscular atrophy) (familial, hereditary) Fazio-Londe disease (Juvenile Progressive Bulbar Palsy) (sporadic, familial) Brown-Vialetto-van Laere syndrome (sporadic, familial) Madras MND (sporadic, familial) FOSMN syndrome*** (sporadic, familial)

ALS: amyotrophic lateral sclerosis; FOSMN: facial-onset sensory and motor neuropathy; MND: motor neuron disease; PLS: primary lateral sclerosis. \*Primary MND group includes distinct clinical conditions which result from primary compromise and neurodegeneration of the lower and/or upper motor neurons; \*\*the classification of Mills' syndrome as an ALS or PLS variant is still a matter of debate; \*\*\*FOSMN is currently included in the group of primary MND, despite its rare occurrence, due to the major neuropathological, laboratory, and neuroimaging evidence linking to ALS-like phenotype and biomarkers.

Spinal Muscular Atrophy (SMA) is the most common group of inherited motor neuronopathies in clinical practice and can present in a wide range of patients including pediatric cases (e.g., neonatal and infancy onset) to late-onset cases (e.g., elderly and adult onset cases)<sup>5,6</sup>. SMA represents a group of inherited neurodegenerative, neurodevelopmental, or neurometabolic disorders that leads to lower motor neuron impairment in a pure pattern (sparing other multisystemic and neurological involvement) or in association with other neurological and multisystemic involvement (SMA-plus or complex phenotypes)<sup>5,6</sup>. The *SMN1*-related SMA (also designated as 5q SMA) comprises the most important clinical and genetic form of SMA, representing the second most common autosomal recessive disorder in clinical practice and including type 1 (Werdnig-Hoffmann disease), type 2 (intermediate or Dubowitz syndrome), type 3 (Kugelberg-Welander disease), and type 4 (adult type)<sup>5,6</sup>. It is estimated a global prevalence of 1 in 10,000 and a carrier incidence of 1 in 50 in the general population<sup>5,6</sup>.

Adult-onset SMA represents a new expanding group of inherited neurodegenerative disorders in clinical practice in the context of late-onset lower MND with pure motor phenotypes or complex systemic and neurological phenotypes. In adult-onset cases, SMA type 4 is the most common type of proximal SMA, and the differential diagnosis with young-onset and juvenile ALS<sup>7</sup> and with non-5q (non-*SMN1*) SMA is important. The non-5q (non-*SMN1*) SMA is an expanding and complex group of more than 15 different clinical and genetic conditions and the target of this review manuscript<sup>3,8</sup>. Proper evaluation and diagnosis of such group of diseases is essential as many of them present as specific potentially treatable conditions that can improve motor and non-motor symptoms, signs, and outcomes. This non-systematic informative and descriptive critical review aims to summarize the most important clinical, genetic, neurophysiologic, and therapeutic aspects about the well-known and established genetic subtypes of adult-onset proximal non-5q SMA.

We have performed a non-systematic review including two distinct strategies using the National Library of Medicine, PubMed search database [last accessed on 28<sup>th</sup> January, 2021], with no delineated period or interval of publication on MEDLINE journals and only including adult patients (with 19 or more years of age). The first search strategy included the Medical Subject Headings (MeSH) term [spinal muscular atrophy] and resulted in 9041 manuscripts, including case reports, editorials, historical articles, journal articles, letters, and reviews. Systematic review and meta-analysis studies were excluded. The first evaluation excluding distal-predominant phenotypes, natural history, therapy-related (experimental) studies and redundant content resulted in 152 manuscripts with significant content regarding proximal SMA presentations with clinical, genetic, and therapeutic purposes. The second parallel search strategy used the term [non-5q spinal muscular atrophy] and included case reports, journal articles, letters, and reviews in adult patients resulting in 18 manuscripts, all of which were previously included in the first search strategy. After a detailed review of the content published in the last 5 years, 13 distinct genetic presentations of non-5q SMA have been identified and are discussed in detail in this review article.

## NON-5Q PROXIMAL SPINAL MUSCULAR ATROPHY

Non-5q SMA is an expanding and heterogeneous group of lower MND due to complex clinical and genetic aspects (Table 2)<sup>3,4,8,9,10,11,12,13</sup>. Up to 5% of all SMA cases result from genetic abnormalities in genes other than *SMN1*<sup>14</sup> and are currently included in this group. Research in the last 20 years resulted in a major expansion in knowledge regarding clinical, pathophysiological, and genetic aspects of different non-5q SMA, especially in the early-onset forms<sup>3,4,8,9,10,11,12</sup>.

**Table 2.** Current classification of adult-onset spinal muscular atrophy with proximal predominance, according to the involved pattern of inheritance<sup>3,4,6,8,9,10,11,12,14</sup>.

Adult-onset SMA with proximal predominance*
<b>I. Autosomal dominant pattern of inheritance</b>
Finkel type SMA (related to <i>VAPB</i> gene variants)
Jokela type SMA (related to <i>CHCHD10</i> gene variants)
Adult-onset scapuloperoneal syndrome linked to <i>TRPV4</i> gene variants
Okinawa type SMA (proximal hereditary sensory and motor neuropathy)
Adult-onset proximal SMA with cardiac involvement ( <i>LMNA</i> variants)
SMA with retained/brisk reflexes (motor neuropathy with pyramidal release signs ( <i>SETX</i> variants)
SMA with lower extremity dominant (SMALED) type 2A – atypical late-onset ( <i>BICD2</i> variants)**
Lower motor neuron disease with respiratory failure associated with <i>MAPT</i> gene variants
<b>II. Autosomal recessive pattern of inheritance</b>
SMA type IV (adult form of 5q SMA)
GM2 gangliosidosis: Adult-onset Tay-Sachs disease (atypical), Sandhoff disease (late adult-onset associated with <i>HEXB</i> variants); AB variant (GM2A activator deficiency)
Late adult-onset primary defects of riboflavin transporter (Fazio-Londe disease and Brown-Vialetto-van Laere syndrome)
Late-onset Spinal Muscular Atrophy associated with Progressive Myoclonic Epilepsy (SMA-PME) due to acid ceramidase deficiency ( <i>ASAHI</i> variants)
Late-onset SMA with Respiratory Distress (SMARD) due to <i>IGHMBP2</i> variants
SMA with lower extremity dominant type 1 – atypical late-onset ( <i>DYNC1H1</i> variants)**
<b>III. X-linked pattern of inheritance</b>
X-linked Spinal and Bulbar Muscular Atrophy (Kennedy's disease)

SMALED: spinal muscular atrophy with lower extremity predominance; \*distal SMA [spinal muscular atrophy] (or distal hereditary motor neuropathy) presentations are not included; \*\*limited data restricted to case reports or small case series.

Most of the new genetic subtypes have been identified during genetic evaluation by whole-exome sequencing (WES) and gene panel testing by next-generation sequencing (NGS) approaches<sup>13</sup>.

Non-5q SMA are commonly classified according to the pattern of inheritance and dominant distribution pattern of weakness (distal SMA, also called distal hereditary motor neuropathy, proximal non-5q SMA, or bulbar-dominant SMA). Adult-onset non-5q SMA can present with two different clinical pictures including: (i) patients with late-onset SMA (slowly progressive lower MND) and negative genetic result for *SMN1/SMN2* gene (pure SMA phenotype); and (ii) autosomal dominant, recessive, or X-linked SMA with other well-defined complex multisystemic or neurological features, including epilepsy, deafness, cerebellar ataxia, or skeletal abnormalities (Table 3)<sup>11,12,14</sup>. This review emphasizes clinical and genetic aspects of adult-onset non-5q proximal SMA (Tables 3 and 4).

**Table 3.** Red-flag signs to consider a possible non-5q (non-*SMN1/SMN2*) form of spinal muscular atrophy<sup>11,12,14</sup>.

Red-flag signs for a non-5q SMA presentation
Disproportionate distal to proximal motor compromise, even in the context of a marked proximal involvement (context of distal hereditary motor neuropathy — distal SMA)
Specific findings and neurological contexts: arthrogryposis multiplex congenita, vocal cord palsy, diaphragmatic palsy with severe early-onset acute respiratory failure, multiple cranial nerve palsy, progressive myoclonic epilepsy, sensorineural hearing loss, mild pyramidal release signs (similar phenotypes to ALS)
Abnormal findings in neuroimaging studies: pontocerebellar hypoplasia, hypomyelination, leukodystrophy, malformations of central nervous system due to abnormal development
Specific neuroophthalmological findings (e.g. cataracts, optic atrophy, retinitis pigmentosa)
Other specific systemic findings (e.g. cardiomyopathy, endocrinopathy)
Familial spectrum of neurological or systemic compromise associated with other red-flag signs for a possible non-5q SMA

SMA: spinal muscular atrophy; ALS: amyotrophic lateral sclerosis.

The main pathophysiological mechanisms related to non-5q SMA involve different complex intracellular dysfunctions (Figure 1), including: (i) defects of neuronal splicing, DNA and protein translation and transcription, and RNA processing and toxic RNA species formation (e.g., *VRK1*, *EXOSC3*, *EXOSC8*, *TSEN54*, *SLC25A6*, *MORC2*, *TRIP4*, *ASCC1*, *UBA1*, *GLE1*, *ERBB3*, *IGHMBP2*, *RBM28*); (ii) defects of pathways of protein aggregation, misfolding, and degradation (regulation of protein quality control, autophagy, and ubiquitin-proteasome system) (e.g., *ASAHI*, *UBA1*, *UBQLN1*, *LYST*, *SCP2*); (iii) defects of axonal transport and cytoskeletal dynamics (e.g., *ASAHI*, *BICD2*, *DYNC1H1*) by distinct mechanisms; (iv) primary defects of ion channels (cation channeling) (e.g., *TRPV4*, *SCN1A*); (v) primary defects of vitamin receptors (uptake) (e.g., *SLC52A2*, *SLC52A3*); and (vi) dysfunction of neuronal mitochondrial energy production and inner structure (functional and structural mitochondrial abnormalities) (e.g., *CHCHD10*, *SCO2*, *TK2*, *DGUOK*)<sup>3,8,9,10,11</sup>. Inherited neurometabolic disorders are also associated with non-5q SMA presentations, including abnormal sphingolipid metabolism, such as in GM2 gangliosidosis and acid ceramidase deficiency<sup>12</sup>.

### Kennedy's disease

In 1968, Kennedy and colleagues described 9 male patients from 2 unrelated families presenting with slowly progressive pure lower MND with onset between 30 to 40 years of age, disclosing bulbar signs (dysphagia, dysphonia, and tongue atrophy and fasciculation), facial and perioral fasciculations and some of them with bilateral gynecomastia<sup>15</sup>. Endocrinopathies and hyperlipoproteinemia were identified in further studies.

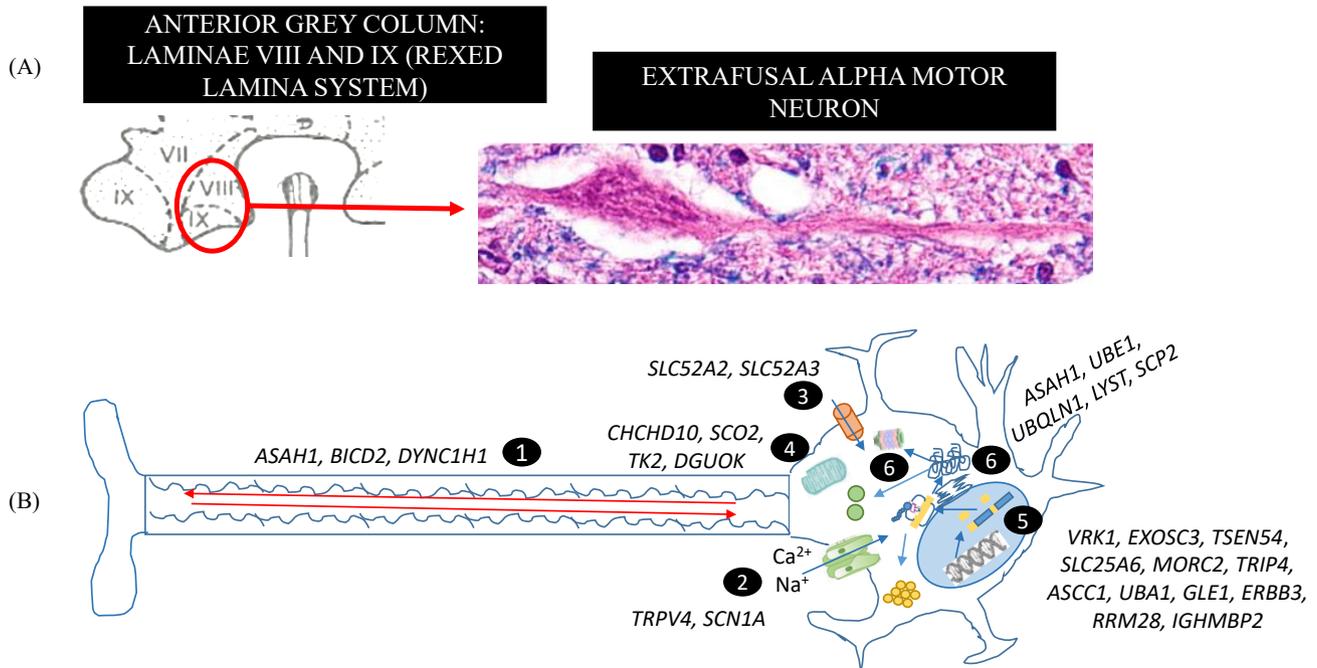
**Table 4.** Clues in the differential diagnosis of suspected genetic basis of proximal spinal muscular atrophy<sup>3,9,10,11,12,14</sup>.

Clinical, neuroimaging and laboratorial clues in the evaluation of suspected proximal SMA	
I. Age at onset	Very early (neonatal or infancy-onset; <2 years): <i>SMN1, SLC52A2, SLC52A3, GLE1, VRK1, GLE1, UBA1, EXOSC8, EXOSC3, TK2*, TRPV4</i> Early (early and late childhood-onset): <i>SMN1, DYNC1H1, BICD2, TRPV4, SLC52A2, SLC52A3, ASAH1, LAS1L, TRPV4</i> Late (juvenile and adult-onset): <i>SMN1, VAPB, TFG, AR, LMNA, SETX, CHCHD10, HEXA, HEXB, GM2A, TRPV4*, ASAH1*, SLC52A2*, SLC52A3*, BICD2*, DYNC1H1*</i>
II. Pattern of inheritance	AR: <i>SMN1, SLC52A2, SLC52A3, HEXA, HEXB, GM2A, ASAH1, VRK1, EXOSC3, EXOSC8, GLE1, IGHMBP2</i> AD: <i>VAPB, TRPV4, TFG, CHCHD10, SETX, LMNA, DYNC1H1, BICD2, GLE1</i> XLR: <i>AR, UBA1, LAS1L</i>
III. LGMW phenotype	Lower extremity predominance: <i>DYNC1H1, BICD2, SMN1, VAPB</i> Scapuloperoneal pattern: <i>TRPV4, SLC52A3*</i> Moderate/severe axial involvement: <i>SMN1, VRK1, AR, SLC52A2*, SLC52A3*</i>
IV. Bulbar-dominant phenotype	Dysphagia/dysphonia: <i>SMN1, AR, SLC52A2, SLC52A3, VRK1, TFG</i> (late stages), <i>HEXB*</i>
V. Multiple cranial neuropathies	Sensorineural hearing loss: <i>SLC52A2, SLC52A3, TRPV4</i> Vocal cord paralysis: <i>TRPV4</i>
VI. Neuro-ophthalmological disturbances	Optic atrophy: <i>SLC52A2, SLC52A3</i> , Pigmentary retinopathy: <i>SLC52A2, SLC52A3</i> ,
VII. Other neurological or neuromuscular compromise	Cerebellar ataxia: <i>SLC52A2, SLC52A3, HEXA, HEXB, GM2A, VRK1</i> Postural tremor/polyminimyoclonus: <i>VAPB, AR, TFG, SMN1, HEXB</i> Parkinsonism/Dystonia: <i>HEXA, HEXB, GM2A</i> Myoclonus/PME: <i>ASAH1, HEXA</i> Cognitive decline: <i>HEXA, HEXB, SLC52A2*, SLC52A3*</i> Intellectual disability: <i>VRK1, EXOSC3, EXOSC8, ASAH1</i> Dysautonomia: <i>VAPB, AR; IGHMBP2</i> Pyramidal signs: <i>SETX, SLC52A2*, SLC52A3*, VAPB*</i>
VIII. Neuroimaging findings	Pontocerebellar hypoplasia: <i>VRK1, EXOSC3, EXOSC8</i> Cerebellar atrophy: <i>SLC52A2, SLC52A3, HEXA, HEXB, GM2A, TK2*</i> Hypomyelination: <i>EXOSC8</i>
IX. Associated neurophysiological findings	Reduced SNAP amplitude: <i>AR, TFG, SLC52A2, SLC52A3</i> Pseudo-myotonic discharges: <i>SMN1*, TFG*</i>
X. Respiratory compromise	Diaphragmatic involvement: <i>IGHMBP2, LAS1L, ASAH1, SMN1, TK2*</i> Restrictive lung disease: <i>UBA1, SMN1, GLE1, TK2*</i>
XI. Miscellaneous	Multiple contracture/arthrogryposis multiplex: <i>GLE1, UBA1, BICD2, DYNC1H1, TRPV4, SMN1*</i> Pes cavus, pes planus: <i>DYNC1H1, BICD2, AR, SLC52A2*, SLC52A3*, TFG*</i> Diabetes and other endocrine diseases: <i>AR, TFG</i> Cardiomyopathy: <i>LMNA, AR</i> High serum CK levels: <i>TFG, AR, VAPB, SMN1, TRPV4*, TK2*</i> Worse prognosis (early death): <i>SMN1, VRK1, EXOSC3, EXOSC8, GLE1, UBA1, TK2*</i> Ancestry (family origin): Japan, Taiwan, South Korea ( <i>TFG, AR</i> ); Brazilian ( <i>VAPB</i> ); Finland ( <i>CHCHD10</i> )

AD: autosomal dominant; AR: autosomal recessive; CK: creatine kinase; LGMW: limb-girdle muscular weakness; PME: progressive myoclonic epilepsy; SMA: spinal muscular atrophy; SNAP: sensory nerve action potential; XLR: X-linked recessive; \*rare finding or rare presentation. All gene symbols are presented in italics.

X-linked spinal and bulbar muscular atrophy (SBMA) or Kennedy's disease (MIM #313200) is an adult-onset X-linked recessive neurodegenerative disorder related to abnormal pathological (CAG) trinucleotide repeat expansion (generally 38–68 CAGs repeats; normal: 11–32 CAGs) in exon 1 in the *AR* gene (Xq12), coding the androgen receptor. Toxic gain of function with polyglutamine repeats and truncated protein formation are associated with neurodegeneration pathogenesis. SBMA is the most common non-5q SMA phenotype worldwide, despite higher prevalence rates in Japan and western Finland due to founder effects<sup>16,17,18,19,20</sup>. Up to 2% of all patients misdiagnosed with ALS have SBMA. Men generally present after the fourth to sixth decade of life with dysphagia, dysphonia, perioral myofasciculations, cramps,

fasciculations in the upper limbs and tongue, and long-standing proximal and symmetrical crural or brachial paraparesis (evolving to quadriparesis) and associated primary myopathy<sup>16,17,18,19,20</sup>. It is classically associated with endocrinopathies (hypogonadism, diabetes mellitus or glucose intolerance, osteopenia, testicular atrophy, oligospermia, and impaired spermatogenesis), gynecomastia, dyslipidemia with nonalcoholic fatty liver disease, risk of cardiac arrhythmia (e.g., Brugada syndrome), and rarely with left ventricular hypertrabeculation/non-compaction cardiomyopathy. Postural and intention tremor involving the hands and distal portion of the upper limbs may occur and presents with characteristics similar to essential tremor, including alcohol and beta-blocker responsiveness. Respiratory failure and



1. Defects of axonal transport and cytoskeletal dynamics (e.g., *ASAH1*, *BICD2*, *DYNC1H1*); 2. Primary defects of ion channels (e.g., *TRPV4*, *SCN1A*); 3. Primary defects of vitamin receptors (e.g., *SLC52A2*, *SLC52A3*); 4. Dysfunction of neuronal mitochondrial energy production and inner structure (e.g., *CHCHD10*, *SCO2*, *TK2*, *DGUOK*); 5. Defects of neuronal splicing, DNA and protein translation and transcription, and RNA processing (e.g., *VRK1*, *EXOSC3*, *TSEN54*, *SLC25A6*, *MORC2*, *TRIP4*, *ASCC1*, *UBA1*, *GLE1*, *ERBB3*, *RRM28*, *IGHMBP2*); 6. Defects of pathways of protein aggregation, misfolding, and degradation (e.g., *ASAH1*, *UBA1*, *UBQLN1*, *LYST*, *SCP2*).

Figure 1. Lower motor neuron anatomical location and structure (A) and non-5q SMA pathophysiological mechanisms (B).

even vocal cord palsy are eventually observed in late stages of disease. Episodic laryngeal stridor and sudden acute respiratory failure may be observed especially during intercurrent infections<sup>16,17,18,19,20</sup>.

Genetic testing by fragment analysis of *AR* gene for pathological CAG repeat expansions is the gold standard procedure for definite diagnosis of SBMA<sup>16,17,18,19,20</sup>. There is a well-established phenomenon of inverted correlation between age of onset and the length of the CAG repeat expansion with marked earlier age at onset in patients with longer repeats. Serum creatine kinase level is commonly mild to moderately elevated, ranging from 650 to 1500 U/L. Muscle biopsy commonly discloses both classic neurogenic and myopathic findings, including vacuolar myopathy, central nuclei, tubular aggregates, and myofibrillar disorganization<sup>16,17,18</sup>. Neurophysiological testing usually shows markedly reduced SNAP (sensory nerve action potentials) amplitude with sub-clinical sensory symptoms and chronic denervation changes, primarily in bulbar and cervical myotomes. Sensory symptoms with distal dysesthesias in the lower limbs and postural tachycardia are more commonly associated with early-onset cases<sup>16,17,18</sup>. Muscle imaging studies have emerged recently in the study of neurogenic conditions such as SBMA and are a potential resource for diagnosis, follow-up of patients<sup>21</sup>, and differential diagnosis with other chronic neurodegenerative conditions such as ALS<sup>22</sup>. Plasma pNfH levels can also give important clues in the differentiation from bulbar-onset ALS, depending on clinical stage, and may become a

possible diagnostic or prognostic biomarker for future studies<sup>23</sup>. Symptomatic heterozygous females with very late-onset (seventh to eighth decade) may present with mild clinical course, cramps, and tongue fasciculations with raised serum creatine kinase (CK) levels<sup>17,19,20</sup>. Long-term treatment with leuprorelin (11.25 mg per dose, once each 12 weeks, subcutaneous use, for up to 84 months) in patients with SBMA during a natural history-controlled study has disclosed a tendency to decrease the progression of the clinical course of motor and bulbar dysfunction, according to ALSFRS-R (ALS Functional Rating Scale-Revised) total score and Limb Norris Score, as well as clinical improvement of dysphagia and lesser occurrence of aspiration pneumonia and death<sup>24</sup>. Leuprorelin is currently a potential therapeutic candidate for patients with mild to moderate motor and bulbar compromise, especially in patients at early clinical stages and without severe respiratory involvement<sup>20</sup>; however, double-blind clinical randomized studies are still necessary. 5alpha-reductase inhibitors have also been studied in few case reports and small case series without marked clinical improvement<sup>25</sup>. A double-blind randomized placebo-controlled trial using intravenous IGF-1 mimetics provided stable muscle volumes during the study period but without improvement of motor function and muscle strength<sup>26</sup>.

In addition, a study reposts a Japanese family with autosomal dominant progressive spinal and bulbar muscular atrophy associated with gynecomastia, upgaze ocular abnormalities, postural tremor, and dysphonia, mimicking

features of Kennedy's disease but with paternal transmission and without pathogenic CAG repeat expansions in *AR* gene. No abnormal autonomic and sensory changes are reported<sup>27</sup>.

### Finkel type spinal muscular atrophy

Finkel type SMA (MIM #182980) is a rare late-onset neurodegenerative lower MND typically found in the Brazilian population, allelic to familial ALS type 8 and linked to the heterozygous pathogenic variant p.Pro56Ser in the *VAPB* (20q13.32) gene, coding the VAMP-associated membrane protein type B. This autosomal dominant adult-onset SMA was originally described by Dr. Nunjo Finkel in 1962, after the analysis of four Brazilian patients (from Guarani town, located in the Zona da Mata, within the state of Minas Gerais) which presented with slowly progressive lower limb weakness, mainly involving the pelvic girdle<sup>28</sup>. It is a long-standing symmetrical lower MND associated with amyotrophy, areflexia, cramps, and postural tremor in distal upper limbs. Most cases present during the third to sixth decade of life with proximal weakness in the lower limbs, evolving after 2 to 3 decades to the upper limbs and respiratory muscle groups. There is marked involvement of abdominal muscle groups with weakness and hypotonia and hyperlordosis<sup>29,30,31,32</sup>. Mildly raised serum CK levels are commonly observed. Needle EMG studies commonly show chronic denervation and reinnervation involving cervical, thoracic, and lumbosacral myotomes, but may also disclose acute denervation, more commonly in earlier onset cases in the third decade of life. Cases with associated upper motor neuron signs generally have more rapid and severe clinical course in the spectrum of familial ALS type 8. Dysautonomic features have also been observed, including chronic constipation, abnormal sudomotor function, sexual dysfunction, sporadic spontaneous choking fits, and suffocation<sup>28,29,30,31,32</sup>.

### Jokela type spinal muscular atrophy

Jokela type SMA (MIM #615048) is an autosomal dominant late-onset lower MND described in the last years associated with mitochondrial dysfunction secondary to heterozygous pathogenic variants in the *CHCHD10* (22q11.23) gene. It has been predominantly described in Finnish families with heterozygous pathogenic variant p.Gly66Val probably due to the founder effect. Most cases start with motor symptoms after the third to fifth decade of life, while cramps and fasciculations may be observed since the third decade of life. It is a pure symmetrical slowly progressive late-onset motor neuronopathy with proximal predominance, diffuse areflexia, fasciculations, myalgia, and painful cramps with only mild bulbar compromise. Head drop and drop attack-like episodes may also be observed and do not correlate with clinical severity<sup>33,34,35,36,37</sup>. Other family members may present with other signs of mitochondrial disease, including eyelid ptosis, cerebellar ataxia, frontotemporal dementia, ALS, atypical parkinsonism, inherited axonal

neuropathy, pes cavus or pes planus, hammertoes, bilateral sensorineural hearing loss, and mitochondrial myopathy<sup>36</sup>. Amyotrophy is more commonly found after two to three decades of clinical involvement<sup>34,35,36,37</sup>, but calf pseudohypertrophy may be also observed<sup>33</sup>. There is marked intrafamilial clinical variability in carriers of p.Gly66Val pathogenic variant, ranging from inherited sensorimotor axonal neuropathy, SMA, and ALS presentation. Upper motor neuron involvement, FTD, and cerebellar ataxia are more commonly observed in patients with the p.Ser59Leu pathogenic variant. Muscle biopsy studies disclose chronic neurogenic findings, distinct large fiber type grouping with non-atrophic type IIA muscle fibers, group atrophy, small groups of highly atrophic rounded type IIA fibers, mitochondrial dysfunction findings, and up to 60% with p62 or TDP-43 positive vacuoles. Muscle MRI shows diffuse fatty degenerative changes, markedly bilateral and in medial gastrocnemius. Serum CK levels are commonly raised up to 8 times above the upper limit of normality<sup>33,32,33,34,35,36,37,38,39,40</sup>.

### TRPV4-associated scapulo-peroneal syndrome

*TRPV4*-associated scapulo-peroneal syndrome or New England type SMA (MIM #181405) in most cases presents as autosomal dominant early-onset SMA with slowly progressive neurogenic scapulo-peroneal weakness and amyotrophy and laryngeal palsy, mimicking features of facioscapulo-humeral muscular dystrophy. Most cases present with non-progressive very early-onset or congenital-onset weakness and knee and ankle contractures with mildly raised serum CK levels. Males are commonly more severely affected than women. Skeletal dysplasia may be also observed in very early-onset cases<sup>11,41,42</sup>. However, late adult-onset cases have been also described with *TRPV4* (12q24.11) gene mutations and related to both distal and proximal predominant phenotypes. Although associated with missense pathogenic variants in autosomal genes, phenotypes become more severe and appear earlier in later generations. Key differential diagnoses include distal SMA and axonal Charcot-Marie-Tooth (CMT) disease. Allelic conditions include CMT type 2C and rare osteomuscular dysplasia and malformation<sup>41,42</sup>.

### Okinawa type spinal muscular atrophy

Okinawa type SMA or hereditary sensory and motor proximal neuropathy (previously known as proximal CMT) (MIM #604484) is associated with heterozygous pathogenic variants in the *TFG* (3q12.2) gene and originates slowly progressive SMA with proximal and lower limb predominance, starting in early adulthood and commonly associated with tremor, cramps, and late sensory neuropathy. Cramps and fatigue commonly precede the onset of proximal muscle weakness and fasciculations involve the truncal and distal portion of the upper limbs. Most typical presentations are associated with the heterozygous pathogenic variant p.Pro285Leu. It is commonly associated with glucose

intolerance, diabetes mellitus, dyslipidemia, and mildly raised serum creatine kinase levels (300-1000 Ui/L). Pes cavus and mild scoliosis are rarely observed<sup>43,44</sup>. Myotonic-like phenomenon and myotonic discharges may also be rarely observed. Despite the occurrence of less severe and later bulbar compromise in Okinawa type SMA, this neurodegenerative disorder should be considered in the differential diagnosis of Kennedy's disease especially in the context of patients with negative genetic testing and autosomal dominant pattern of inheritance, similar clinical phenotypes, marked compromise of sensory nerve action potential amplitude, and positive epidemiologic and family histories for Okinawa's ancestry. Its major representative ethnic group of patients is from Japan (from Kansai and Okinawa region), South Korea, Taiwan, and Brazilian patients from Japanese ancestry. Allelic conditions include autosomal recessive hereditary spastic paraplegia type 57 (SPG57) and extraskeletal myxoid chondrosarcoma<sup>43,44,45,46</sup>.

### Adult-onset GM2 gangliosidosis

GM2 gangliosidosis is a complex and classical inherited neurometabolic group of disorders resulting from inborn errors of metabolism with beta-hexosaminidase A or B deficiencies. GM2 gangliosidosis results from mutations in the coding genes of alpha subunit (*HEXA*), beta subunit (*HEXB*), or GM2 gangliosidosis coactivator (*GM2A*) of hexosaminidases A and B, leading to abnormal lysosomal storage of neuronal glycosphingolipids. Neurological presentations of GM2 gangliosidosis include infantile, juvenile, and adult late-onset cases. Regarding its biochemical basis, three neurometabolic phenotypes can be recognized: Tay-Sachs disease (isolated deficiency of hexosaminidase A), Sandhoff disease (combined deficiency of hexosaminidases A and B), and GM2 activator deficiency. Despite the existence of atypical late-onset Tay-Sachs disease of the adult (MIM #272800) presenting with isolated cerebellar ataxia or pure symmetrical slowly progressive SMA resulting from homozygous or compound heterozygous mutations in the *HEXA* (15q23) gene or *GM2A* (5q33.1) gene in the GM2 activator deficiency (MIM #272750), late-onset lower MND presentation has been more widely described in association with adult-onset Sandhoff disease (MIM #268800) with compound heterozygous or homozygous pathogenic variants in the *HEXB* (5q13.3) gene<sup>47</sup>. It is uncommon in late-onset cases of both Tay-Sachs disease and Sandhoff disease the occurrence of cherry-red spots, seizures, or the progressive myoclonic epilepsy phenotype. Late-onset cases may be clinically undistinguishable from juvenile ALS or SMA type IIIb/IV, however more commonly involves triceps brachii and intrinsic muscles of the hand in the upper limbs. Late-onset GM2 gangliosidosis may be also associated with saccadic dysmetria, abnormal vertical and horizontal pursuit, low angular vestibulo-ocular reflex, cerebellar ataxia, cognitive decline, parkinsonism, and cerebellar cognitive affective syndrome during disease course<sup>47</sup>.

Pyramidal release signs may be observed in late-onset cases, but usually with associated cerebellar ataxia or lower MND. Neuropsychiatric disturbances including psychosis, anxiety, and depression are frequently observed, even in early stages of disease. Rare adult-onset presentations of Sandhoff disease with pure lower motor neuron (LMN) include brachial amyotrophic diplegia<sup>48</sup> and bulbosplinal neuronopathy with bilateral facial weakness, dysarthria, dysphagia, and postural tremor, mimicking features of Kennedy's disease<sup>49</sup>. Neuroimaging studies generally disclose cerebellar atrophy (even in cases without cerebellar ataxia), variable cortical atrophy, and absence of thalamic signal changes commonly observed in infantile-onset cases. Needle EMG discloses chronic diffuse denervation and reinnervation signs, while nerve conduction studies show moderate reduction of SNAP amplitudes. General prognosis is better in late-onset cases if compared to infantile and juvenile-onset presentations, commonly with normal life span<sup>12,47,49,50,51</sup>.

### LMNA-associated spinal muscular atrophy

Adult-onset proximal SMA with cardiac involvement results from heterozygous mutations in the *LMNA* (1q22) gene, coding the prelamin A/C, and is characterized by autosomal dominant SMA starting between 35 and 65 years of age, with symmetrical, slowly progressive and proximal predominance, associated lately with variable degrees of cardiomyopathy, including atrioventricular blocks, atrial fibrillation, and dilated cardiomyopathy. Serum CK levels are commonly unremarkable in most cases. Needle EMG includes mixed chronic denervation and reinnervation findings and mild myopathic features, while targetoid-fibers and type grouping are commonly observed in muscle biopsy. More than 10 different allelic clinical conditions have been described, including autosomal dominant or recessive Emery-Dreifuss muscular dystrophy, congenital muscular dystrophy, limb-girdle muscular dystrophy type 1B, Hutchinson-Gilford progeria, CMT type 2B1, and different syndromic and non-syndromic restrictive or dilated cardiomyopathies<sup>11,52,53</sup>.

### Hereditary motor neuropathy with pyramidal features

Hereditary motor neuropathy with pyramidal features (also called SMA with retained reflexes) is a rare neurodegenerative condition due to heterozygous pathogenic variants in the *SETX* gene (9q34.13), coding neuronal senataxin, and is associated with autosomal dominant slowly progressive symmetrical SMA with distal and proximal involvement combined with brisk tendon reflexes or pyramidal release signs. Bulbar and cognitive dysfunction are not observed until very late stages of disease. Allelic conditions include familial ALS type 4 (juvenile ALS type 4) and oculomotor apraxia type 2. Some authors include both juvenile ALS type 4 and hereditary motor neuropathy with pyramidal features as overlapping and undistinguishable clinical conditions<sup>1,54,55</sup>.

### Adult-onset atypical spinal muscular atrophy with lower extremity predominance

SMA with lower extremity predominance type 1 (SMALED1) (MIM #158600) is a rare early-onset slowly progressive SMA that presents with marked proximal and lower limb predominance. Distal involvement with pes planus or cavus may be also observed, especially in early-onset cases. Cognitive compromise, delayed motor milestones and polymicrogyria and other neuronal migration defects are commonly observed in early-onset cases. However, atypical adult-onset and juvenile-onset cases have been also associated with pathogenic variants in the *DYNC1H1* gene (14q32.31) and with slowly progressive clinical course, similar to extremely rare adult-onset presentations of autosomal dominant SMALED type 2A (MIM #615290) due to *BICD2* gene (9q22.31) with joint contractures<sup>56,57,58,59</sup>. Late-onset cases with proximal upper limb involvement have also been described. There is marked clinical overlap with CMT phenotype, and some patients remain misdiagnosed with an inherited neuropathy during decades until a definite neurophysiological study discloses almost normal SNAPs. Allelic conditions include CMT type 2O, cortical neuronal migration defect with intellectual disability and congenital MND with isolated cortical malformation<sup>56,57,58,59</sup>.

### Late-onset primary riboflavin transporter deficiency (*SLC52A2*, *SLC52A3*)

Late-onset (or adult form) of both Fazio-Londe disease and Brown-Vialetto-van Laere syndrome (MIM #211530, #614707) are typical clinical presentations of primary riboflavin transporter deficiency in the gut, central nervous system, or blood-brain barrier due to homozygous or compound heterozygous pathogenic variants in the *SLC52A2* (8q24.3) or *SLC52A3* (20p13) genes<sup>60,61</sup>. Despite global distribution with familial aggregates in Arabic, Scottish, Italian, Lebanese, and Pakistani families and occurrence in both sexes, there is female predominance in sporadic and familial cases. Both conditions typically give rise to autosomal recessive SMA with bulbar, facial and symmetrical and proximal involvement of the upper limbs, sometimes associated with cerebellar ataxia, sensorimotor axonal neuropathy, scoliosis, optic atrophy, retinitis pigmentosa, psychiatric disturbances, and sensorineural deafness (exclusively associated with Brown-Vialetto-van Laere syndrome and commonly preceding motor symptom-onset), evolving lately with dropped head syndrome and severe respiratory insufficiency<sup>60,61,62,63</sup>. Late-onset phenotypes are associated with slowly progressive clinical course, whilst early adulthood phenotypes present commonly with more rapidly progressive bulbar symptoms. However, rapidly progressive bulbar and facial involvement responsive to riboflavin supplementation has been reported in adult-onset cases, mimicking bulbar-onset ALS. The occurrence of multiple lower cranial nerve palsies (mainly VII, IX, and XII cranial nerves) gives a major clue to

consider riboflavin transporter defects as a possible diagnosis<sup>60,61,62,63</sup>. The main differential diagnosis for most cases include juvenile or young-onset bulbar-onset ALS, sporadic progressive bulbar palsy (especially in female cases), Madras MND, FOSMN (facial-onset sensory and motor neuropathy) syndrome, Finnish type hereditary amyloidosis (amyloid cranial neuropathy with lattice corneal dystrophy type II), Worster-Drought syndrome, Boltshauser syndrome and Nathalie syndrome<sup>60,61,62,63</sup>. Riboflavin transporter defects are potentially treatable inherited neurometabolic disorders, which can be associated with variable degrees of clinical and neurophysiological response to high therapeutic doses of oral riboflavin supplementation (10-20 mg/kg/day). Regarding metabolic profile studies, acylcarnitine profiles commonly present abnormal testing with similar patterns observed also in MADD (multiple acyl-CoA dehydrogenase deficiency) or glutaric aciduria type II and sometimes with secondary carnitine deficiency<sup>12,60,61,62,63</sup>.

### Lower motor neuron disease with respiratory failure associated with *MAPT* gene mutations

This autosomal dominant tauopathy was described in large non-consanguineous Italian kindred, resulting from a heterozygous pathogenic variant p.Asp348Gly in the *MAPT* gene (17q21.31), coding the microtubule-associated protein Tau, involved with axonal transport and microtubule functions. All patients presented with adult-onset proximal symmetric weakness of the upper limbs and prominent early respiratory failure. None of the patients presented with signs suggestive of frontotemporal lobar degeneration or its variants<sup>64</sup>. This same gene mutation was identified also in an Italian female patient with LMN-dominant ALS with long-lasting disease course, mild Parkinsonism, and early respiratory failure<sup>65</sup>. This clinical-genetic subtype added intraneuronal tau degradation and its related pathways to the pathophysiological understanding of lower motor neuron degeneration and the potential role of neurofibrillary tangles with hyperphosphorylated tau protein as potential neuropathological biomarkers of this non-5q SMA. Neuropathological studies disclosed accumulated phosphorylated tau protein in the surviving lower motor neurons and reduction of neurite length and arborization from alpha-motoneuron. Allelic disorders include Frontotemporal lobar degeneration with MND or Parkinsonism, and progressive supranuclear palsy<sup>64,65</sup>.

### Late-onset spinal muscular atrophy associated with progressive myoclonic epilepsy due to acid ceramidase deficiency

Autosomal recessive non-5q SMA associated with N-acylsphingosine amidohydrolase 1 (acid ceramidase) deficiency is due to homozygous or compound heterozygous pathogenic variants in *ASAHI* gene (8p22). Most cases have onset during the first two decades of life, generally with

proximal lower limb weakness and hypotonia due to lower motor neuron disease, followed by upper limb involvement, postural tremor, myoclonus and progressive myoclonic epilepsy during the second or third decade of life. Poliarticular arthritis, eyelid myoclonic status epilepticus, absence epilepsy with atonic seizures, and sensorineural deafness may also be observed. Myoclonic epilepsy is commonly resistant to conventional drug therapy. EEG generally discloses sub-cortical myoclonic epileptic discharges sensitive to hyperventilation. Atypical presentations with pure lower motor neuron syndrome or pure myoclonic epilepsy have been also identified. Mild adult-onset presentations without seizures or myoclonus have been also described. Allelic conditions include Farber lipogranulomatosis<sup>12,66</sup>.

### Late-onset spinal muscular atrophy with respiratory distress due to *IGHMBP2* mutations

This autosomal recessive presentation commonly originates in childhood with diaphragmatic palsy, dysautonomic features, sensory polyneuropathy, and symmetrical distal and proximal SMA due to compound heterozygous or homozygous pathogenic variants in the *IGHMBP2* gene (11q13.3), coding the helicase immunoglobulin mu DNA-binding protein 2. Neonatal presentations are commonly fatal during the first year of life. Late-onset phenotypes have been rarely described with mild distal and proximal motor involvement, but in some cases associated with early scoliosis and diaphragmatic palsy. Important intrafamilial variability is observed in some cases, especially in those with associated

sensorimotor axonal polyneuropathy. Allelic conditions include CMT type 2S, distal hereditary motor neuronopathy type VI, and infantile-onset SMARD<sup>67,68</sup>.

### A practical diagnostic approach and flowchart for suspected cases of adult-onset non-5Q proximal spinal muscular atrophy

Adult-onset non-5q SMA is a complex and genetically heterogeneous group of neurodegenerative and neuro-metabolic disorders. A diagnostic flowchart can be applied to suspected cases of adult-onset proximal SMA (Figure 2) for a detailed and more precise symptom and sign-based approach to a definite diagnosis of these complex clinical conditions<sup>9,10,11,12,14</sup>. Clinical, laboratorial, neurophysiological, and neuroimaging clues (Table 4) are the best way to rule out other important differential diagnoses in LMN syndrome (pure SMA and SMA-plus phenotypes) and provide key information for the best cost-effective diagnostic work-up<sup>3,9,10,11,12,14</sup>. Due to the complex expanding genetic and clinical spectrum of non-5q proximal SMA, next-generation sequencing-based approaches (or massively parallel sequencing technologies) including whole-exome sequencing or targeted sequencing panels represent the main definitive diagnostic methods for most cases<sup>13</sup>, although specific genetic testing with Sanger sequencing, hotspot analysis, and single gene sequencing is still essential in certain clinical settings (e.g., highly specific phenotypes or populations with specific variants due to founder effects)<sup>9,10,11,14</sup>. A proper definite diagnosis of the underlying genetic basis is essential to provide specific

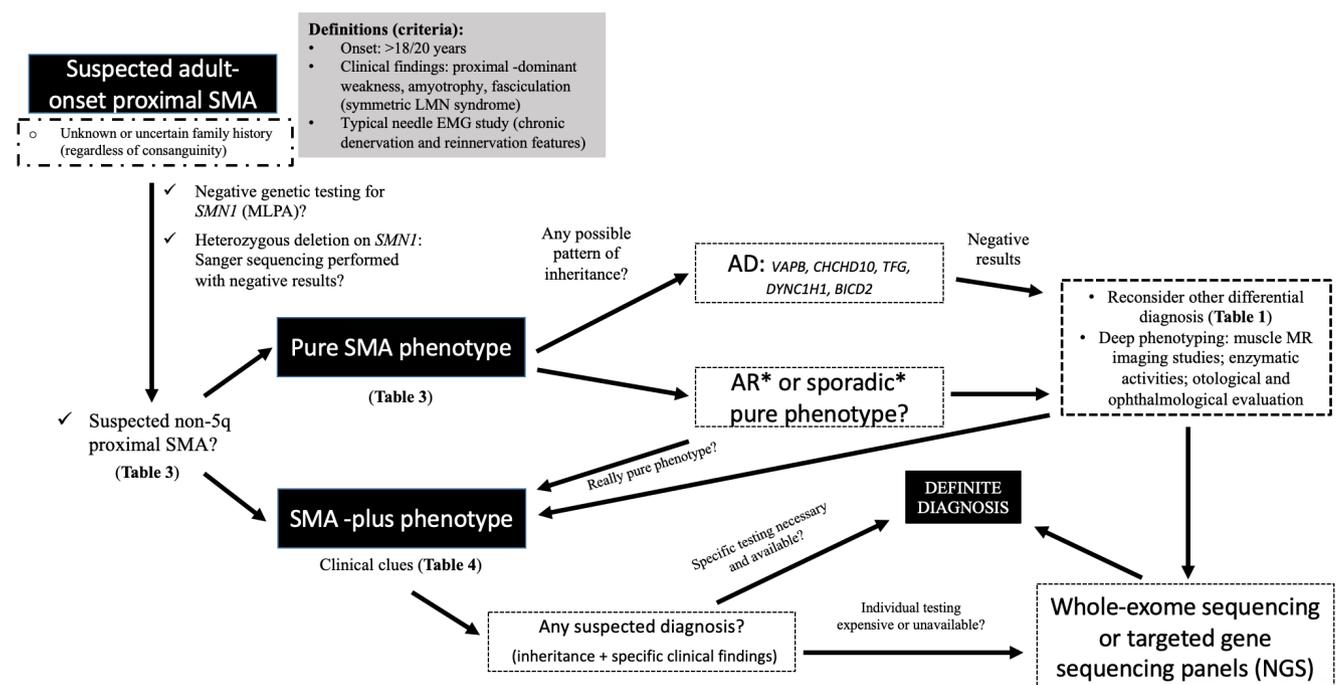


Figure 2. Diagnostic flowchart for suspected cases of adult-onset proximal spinal muscular atrophy.

disease-modifying therapies, especially at early stages of the clinical course, aiming better prognosis and more significant clinical outcomes.

Late adult-onset SMA is a new expanding group of inherited neurodegenerative disorders in clinical practice which arise in the context of a major differential diagnosis of adult

lower MND with pure motor phenotypes or complex systemic and neurological phenotypes. Proper evaluation and diagnosis of such group of diseases is essential as many of them present with specific potentially treatable pathophysiological dysfunction which can improve motor and non-motor symptoms and signs.

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