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REVIEW ARTICLE

Clinical and genetic diversity of *SMN1*-negative proximal spinal muscular atrophies

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Hereditary spinal muscular atrophy is a motor neuron disorder characterized by muscle weakness and atrophy due to degeneration of the anterior horn cells of the spinal cord. Initially, the disease was considered purely as an autosomal recessive condition caused by loss-of-function *SMN1* mutations on 5q13. Recent developments in next generation sequencing technologies, however, have unveiled a growing number of clinical conditions designated as non-5q forms of spinal muscular atrophy. At present, 16 different genes and one unresolved locus are associated with proximal non-5q forms, having high phenotypic variability and diverse inheritance patterns. This review provides an overview of the current knowledge regarding the phenotypes, causative genes, and disease mechanisms associated with proximal *SMN1*-negative spinal muscular atrophies. We describe the molecular and cellular functions enriched among causative genes, and discuss the challenges in the post-genomics era of spinal muscular atrophy research.

Keywords: SMA; molecular genetics; clinical characteristics

Abbreviations: ALS = amyotrophic lateral sclerosis; HMSN = hereditary motor and sensory neuropathy; SMA = spinal muscular atrophy; SMA-LED = SMA with lower extremity predominance; SMA-PME = SMA with progressive myoclonic epilepsy; SMA-RD = SMA with respiratory distress; SMA-X = X-linked SMA

Introduction

Inherited spinal muscular atrophy (SMA) was first recognized as a distinct disease entity with a spinal nature at the end of the 19th century (Hoffmann, 1893; Werdnig, 1891). This neuromuscular disorder is caused by degeneration of anterior horn cells of the spinal cord, leading to symmetric muscle weakness and atrophy. Initially, SMA was considered to be an exclusively autosomal recessive condition, classified into four types based upon disease severity and onset age (OMIM 253300, 253550, 253400, and 271150) (Harding and Thomas, 1980). The disease was mapped to chr5q13, and 20 years ago *SMN1* was identified as the causal gene (Lefebvre *et al.*, 1995). Deletions and point mutations in *SMN1* cause loss of survival of motor neuron protein, resulting in anterior horn cell degeneration.

Although genetic diagnosis was achieved for the majority of patients with SMA after identification of *SMN1*, a small proportion (4%) seemed to be unlinked to chr5q13 (Wirth, 2000). In recent years, the number of causative genes associated with non-5q SMA has expanded rapidly due to the advent of next generation sequencing technologies. Although very rare, non-5q SMA forms are clinically and genetically heterogeneous. They are usually

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classified on the basis of inheritance pattern (autosomal dominant, autosomal recessive or X-linked) and distribution of muscle weakness (proximal, distal or bulbar) (Darras, 2011). SMA with predominant distal involvement largely overlaps with distal hereditary motor neuropathies. Here, we will review only the proximal types of SMA, because the distal forms are substantially covered elsewhere (Rossor *et al.*, 2012).

No cure for SMA is currently available and treatment is symptomatic and supportive. Physical therapy and rehabilitation to slow muscle atrophy may be helpful. Severe forms of the disorder can be lethal from an early age due to respiratory insufficiency. Patients with milder forms are disabled due to muscle weakness and wasting, and they may eventually become wheelchair-bound. Thus, there is an urgent need to establish a more thorough understanding of the disease-associated molecular mechanisms that could lead to potential causal treatments.

Clinical features

The diagnosis of proximal SMA can be challenging, as the clinical spectrum may vary from early infant death to normal adult life with mild muscle weakness. A detailed medical history and thorough neurological examination are highly informative for the clinical diagnosis. The trait of inheritance is not always straightforward, due to sporadic patients who may harbour *de novo* mutations, or non-paternity. To reflect this limitation, in this review we will present the different SMA forms according to their age at onset (Table 1). Early-onset conditions are defined as disorders with clinical symptoms that begin in infancy or childhood, whereas late-onset conditions appear in adolescence or adulthood.

The clinical hallmark of proximal SMA is symmetrical muscle weakness, more pronounced for proximal than distal limb muscles, and generally affecting the legs more than the arms (D'Amico *et al.*, 2011). The clinical course ranges from static to rapidly progressive, leading to respiratory distress requiring mechanical ventilation. Sensitivity is spared, while deep tendon reflexes can vary from absent to brisk, depending on form, age at onset and duration of the disease. In most cases intellect is preserved.

The first step in the diagnosis of SMA is to differentiate motor neuron disease from other disorders with similar clinical features. The most important differential diagnostic conditions for an infant presenting with hypotonia and weakness are congenital myopathies and muscular dystrophies, congenital myotonic dystrophy, congenital myasthenic syndromes, metabolic myopathies, congenital disorders of the motor neuron and the peripheral nerve (congenital hypomyelinating neuropathy), as well as non-neuromuscular conditions, including acute hypoxic ischaemic encephalopathy, neonatal sepsis and dyskinetic or metabolic conditions (D'Amico *et al.*, 2011). Proximal muscle weakness in adulthood can occur in limb-girdle muscular dystrophies, metabolic, mitochondrial myopathies, hexosaminidase A deficiency and amyotrophic lateral sclerosis (ALS).

If history and neurological examination are suggestive of motor neuron disease, multiple tests are performed at a second stage. These include (i) laboratory exams, measuring serum creatine phosphokinase levels; and (ii) electrophysiological tests, such as EMG and nerve conduction studies.

In the case of motor unit involvement, genetic testing of *SMN1* needs to be pursued first. After exclusion of *SMN1* deletions or point mutations, other motor neuron disorders such as non-5q SMA and ALS should be considered. In the case of early-onset anterior horn impairment, additional features, such as arthrogryposis, myoclonic epilepsy, sensorineural deafness, or pontocerebellar hypoplasia should be investigated. The late-onset forms of proximal non-5q SMA, especially with preserved or brisk tendon reflexes, are difficult to differentiate from the growing list of familial and sporadic ALS forms, where involvement of upper and lower motor neurons is typical (Baumer *et al.*, 2014).

Early-onset conditions

Early-onset scapuloperoneal spinal muscular atrophy

Major signs and symptoms

The main features of scapuloperoneal SMA include congenital to childhood onset, progressive scapuloperoneal atrophy, laryngeal palsy with hoarse voice and respiratory stridor (DeLong and Siddique, 1992; Isozumi *et al.*, 1996; Berciano *et al.*, 2011). Generally, muscle weakness is proximal in the upper limbs and distal in the lower limbs; however, a case with leading proximal muscle weakness in all four limbs has also been described (DeLong and Siddique, 1992). Motor development can be delayed in some cases, but intellect is normal. Electrophysiological studies show reduced compound muscle action potentials with normal nerve conduction velocities. Muscle biopsies reveal grouped fibre atrophy, consistent with a neurogenic process.

Causative gene

Scapuloperoneal SMA is an autosomal dominant disease caused by missense mutations in *TRPV4*, encoding transient receptor potential cation channel, subfamily V, member 4 (Deng *et al.*, 2010).

Allelic disorders

TRPV4 mutations cause a broad spectrum of disorders, affecting not only the nervous system, but also bone formation. In terms of neurological involvement, three partially overlapping phenotypes are reported, namely scapuloperoneal SMA, distal spinal muscular atrophy, and hereditary motor and sensory neuropathy type 2C (HMSN2C) (Auer-Grumbach *et al.*, 2010; Deng *et al.*, 2010; Landoure *et al.*, 2010). These different phenotypes may even occur within the same family (Auer-Grumbach *et al.*, 2010) and might have an incomplete penetrance (Berciano *et al.*, 2011). In addition, heterozygous *TRPV4* mutations are responsible for various skeletal dysplasias (Nishimura *et al.*, 2012).

Functional studies into the disease mechanism

TRPV4 forms a non-selective calcium channel that plays a role in neural signalling (Liedtke, 2008). The disease mechanism by which *TRPV4* mutations cause different neuronopathies is under debate

Table 1 Currently known disease genes and loci for proximal *SMN1*-negative spinal muscular atrophies

Type (OMIM #)	Gene	Locus	Inheritance	Phenotype	Clinical features	Allelic disorders
Early onset						
SPSMA (181405)	*TRPV4*	12q24.11	AD	Scapuloperoneal spinal muscular atrophy	Progressive scapuloperoneal muscle weakness, laryngeal palsy	Congenital dSMA, CMT2C, AD brachyolmia
SMALED1 (158600)	*DYNC1H1*	14q32.31	AD	Lower extremity-predominant spinal muscular atrophy-1	Muscle weakness affecting proximal lower extremities and sparing upper limbs	CMT2O, malformations of cortical development, mental retardation
SMALED2 (615290)	*BICD2*	9q22.31	AD	Lower extremity-predominant spinal muscular atrophy-2	Muscle weakness affecting proximal lower extremities and sparing upper or early-onset contractures, upper motor neuron involvement	Late onset HSP
LAAHD (611890)	*GLE1*	9q34.11	AR	Arthrogryposis with anterior horn cell disease	Foetal immobility, hydrops, micrognatia, pulmonary hypoplasia, pterygia and multiple joint contractures, prenatal akinesia	Lethal congenital contracture syndrome 1
SMAX2 (301830)	*UBA1*	Xp11.23	XR	Lethal infantile spinal muscular atrophy, with arthrogryposis	Hypotonia, areflexia, chest deformities, facial dysmorphic features, congenital joint contractures, bone fractures, genital abnormalities	
SMAPME (159950)	*ASAH1*	8p22	AR	Spinal muscular atrophy with progressive myoclonic epilepsy	Refractory to treatment myoclonic epilepsy, dysphagia, respiratory muscle weakness	Farber lipogranulomatosis
PCH1A (607596)	*VRK1*	14q32.2	AR	Pontocerebellar hypoplasia with infantile spinal muscular atrophy	Pontocerebellar hypoplasia, microcephalia, mental retardation, early death	
PCH1B (614678)	*EXOSC3*	9p13.2	AR	Pontocerebellar hypoplasia with infantile spinal muscular atrophy	Pontocerebellar hypoplasia, microcephalia, mental retardation, early death	
BVVLS1 (211530)	*SLC52A3*	20p13	AR	Brown-Vialetto-Van Laere syndrome 1	Ponto-bulbar palsy, bilateral sensorineural hearing loss	Fazio-Londe disease
BVVLS2 (614707)	*SCL52A2*	8q24.3	AR	Brown-Vialetto-Van Laere syndrome 2	Ponto-bulbar palsy, bilateral sensorineural hearing loss	Fazio-Londe disease
Late onset						
SMAFK (182980)	*VAPB*	20q13.32	AD	Late-onset spinal muscular atrophy, Finkel type	Muscle cramps and fasciculations	Typical and atypical amyotrophic lateral sclerosis, skeletal dysplasia
–	*HEXB*	5q13.3	AR	Late adult-onset pure spinal muscular atrophy	Proximal muscle weakness of the lower limbs	Sandhoff disease
SMAJ (615048)	–	22q11.2-q13.2	AD	Spinal muscular atrophy, Jokela type	Painful cramps and fasciculations	
ALS4 (602433)	*SETX*	9q34	AD	Juvenile to adult onset SMA with pyramidal features	Proximal and distal muscle weakness, hand tremor, brisk tendon reflexes	Ataxia oculomotor apraxia, ataxia-tremor, juvenile ALS4, distal hereditary motor neuronopathy with pyramidal features
LGMD1B (159001)	*LMNA*	1q22	AD	Adult-onset proximal spinal muscular atrophy followed by cardiac involvement	Progressive proximal muscle weakness and cardiomyopathy	Cardiomyopathy, dilated 1A, CMT2B1, Emery-Dreifuss muscular dystrophy 2, congenital muscular dystrophy, limb-girdle muscular dystrophy type 1B, Slovenian type heart-hand syndrome, Hutchinson-Gilford progeria, partial lipodystrophy, mandibuloacral dysplasia
HMSNP (604484)	*TFG*	3q12.2	AD	Proximal hereditary motor and sensory neuropathy, Okinawa type	Mild sensory involvement, painful muscle cramps, myotonia in hands, dysphagia	
SMAX1 (313200)	*AR*	Xq12	XR	Kennedy disease, spinal and bulbar muscular atrophy	Proximal, bulbar weakness, endocrine impairment	Androgen insensitivity syndrome

AD = autosomal dominant; AR = autosomal recessive; CMT = Charcot–Marie–Tooth; XR = X-linked recessive; HSP = hereditary spastic paraplegia; dSMA = distal SMA.

and no clear genotype–phenotype correlations have been established to date (Zimon *et al.*, 2010). One study reports that missense mutations affecting the ankyrin domain of the protein—including scapuloperoneal SMA-causing mutations—reduce surface expression of the channel, with the formation of cytoplasmic aggregates and loss of normal channel function (Auer-Grumbach *et al.*, 2010). However, other reports show increased intracellular calcium levels due to abnormal channelling activity (Deng *et al.*, 2010; Landoure *et al.*, 2010). It has been suggested that the vast phenotypic variability is due to differential effects on regulatory protein-protein interactions (Landoure *et al.*, 2010; Zimon *et al.*, 2010).

Animal models

A mouse model lacking TRPV4 does not show apparent neuromuscular abnormalities (Liedtke and Friedman, 2003; Suzuki *et al.*, 2003). These data suggest that the disease phenotype does not result from loss of normal channel function, adding to arguments that favour a gain-of-function mechanism.

Spinal muscular atrophy with lower extremity predominance

Major signs and symptoms

Spinal muscular atrophy with lower limb predominance (SMA-LED) is an early-onset static or slowly progressive disorder, characterized by proximal muscle weakness and atrophy predominantly affecting the lower extremities, with mild to absent upper limb involvement (Harms *et al.*, 2010, 2012; Tsurusaki *et al.*, 2012; Neveling *et al.*, 2013; Oates *et al.*, 2013; Peeters *et al.*, 2013). The disease does not cause severe disability, as patients remain ambulatory even until the sixth decade. Tendon reflexes in the four limbs vary from decreased to brisk, combined with extensor plantar reflexes (Neveling *et al.*, 2013; Oates *et al.*, 2013; Peeters *et al.*, 2013). Skeletal deformities range from lumbal hyperlordosis and scapular winging to severe hip dislocation, lower limb contractures and deformities (Fig. 1). Nerve conduction studies are normal. EMG and skeletal muscle biopsies indicate chronic denervation and reinnervation.

Causative genes

SMA-LED type 1 is an autosomal dominant condition caused by mutations in the heavy chain of cytoplasmic dynein (*DYNC1H1*). Currently, four heterozygous missense mutations in the DYNC1H1 tail region are associated with SMA-LED1 (Harms *et al.*, 2010; Tsurusaki *et al.*, 2012).

The causative gene for SMA-LED type 2 is bicaudal D homolog 2 (*Drosophila*) (*BICD2*). Seven heterozygous missense mutations have been reported, positioned within the three coiled-coil domains of BICD2 (Neveling *et al.*, 2013; Oates *et al.*, 2013; Peeters *et al.*, 2013; Synofzik *et al.*, 2014). The p.S107L hotspot mutation was found in five families with different ethnicity, with one proven *de novo* occurrence.

Allelic disorders

The SMA-causing p.H306R mutation in *DYNC1H1* was also found in a family with axonal Charcot–Marie–Tooth disease type 2O (CMT2O) (Weedon *et al.*, 2011). Furthermore, mutations in *DYNC1H1* cause mental retardation with cortical neuronal migration defects (Vissers *et al.*, 2010; Willemsen *et al.*, 2012; Poirier *et al.*, 2013). Some *DYNC1H1* mutations lead to a combined phenotype of congenital motor neuron disease and cortical malformation, supporting a continuum of clinical presentation (Fiorillo *et al.*, 2014).

For BICD2, one missense mutation (p.K508T) in the kinesin-binding middle coil is reported to cause hereditary spastic paraplegia (Oates *et al.*, 2013). Furthermore, a family was reported with late-onset SMA (between 40–65 years) characterized by more pronounced distal lower limb weakness (Synofzik *et al.*, 2014).

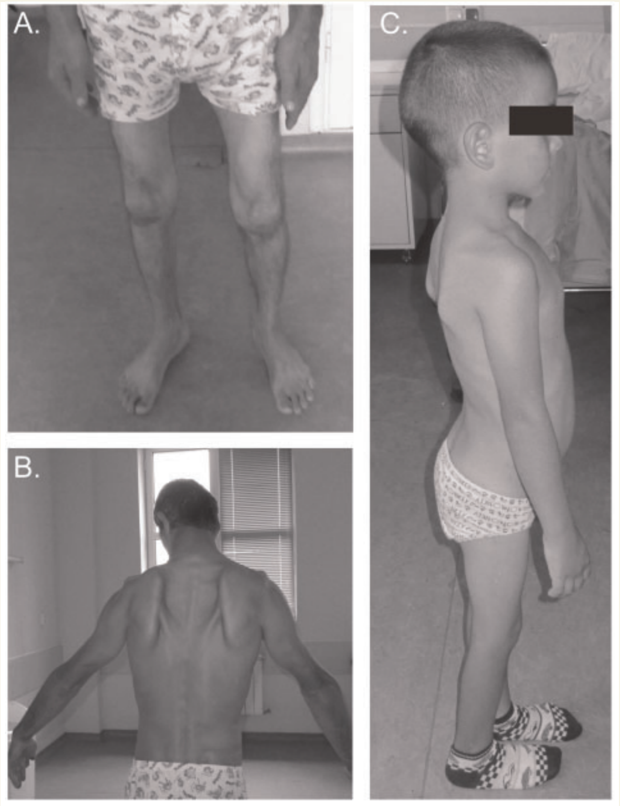

Figure 1 The clinical features of patients with lower extremity-predominant SMA (SMALED2) with mutations in *BICD2*. (**A**) Hypotrophy of proximal and distal muscles of the lower limbs. (**B**) Scapular winging. (**C**) Lumbal hyperlordosis.

Functional studies into the disease mechanism

The dynein heavy chain (DYNC1H1) is responsible for the assembly of all components of the dynein motor and for ATPase-dependent retrograde movement of the complex along microtubules. Functional characterization of the SMA-causing p.I584L mutation revealed reduced dynein stability and microtubule binding during ATP hydrolysis (Harms *et al.*, 2012). Two mutations causing cortical malformations and clinical signs of peripheral neuropathy (p.K3336N, p.R3384Q) located in the microtubule-binding stalk, substantially decrease microtubule binding affinity (Poirier *et al.*, 2013). For p.N1194R and p.E3048K, causing a combined phenotype, Golgi reassembly following microtubule depolymerization is delayed, but stability and microtubule binding capacity appear normal (Fiorillo *et al.*, 2014).

BICD2 functions as an adaptor of the dynein molecular motor and comprises three coiled-coil domains that interact with different motor components (Hoogenraad *et al.*, 2001, 2003; Matanis *et al.*, 2002; Splinter *et al.*, 2010). The N-terminal domain strongly binds to dynein, whereas the C-terminal recognizes various cargos, such as RAB6A. The middle coil is believed to have a regulatory function and mildly interacts with kinesin (KIF5B) (Grigoriev *et al.*, 2007). Alterations in the different domains have differential effects on BICD2 properties. N-terminally altered BICD2 exhibits increased binding to dynein (Oates *et al.*, 2013; Peeters *et al.*, 2013), accumulates at the microtubule organizing complex (Peeters *et al.*, 2013) and leads to Golgi fragmentation (Neveling *et al.*, 2013; Peeters *et al.*, 2013), a hallmark of impaired retrograde transport. An alteration in the middle coil (p.R501P) causes enhanced dynein binding and perinuclear ring-like accumulation, co-localizing with RAB6A (Oates *et al.*, 2013). C-terminally altered BICD2 exhibits reduced interaction with the cargo protein RAB6A (Peeters *et al.*, 2013), but Golgi fragmentation is not consistent for all C-terminal BICD2 mutations (Neveling *et al.*, 2013; Peeters *et al.*, 2013). Although the net outcome of these BICD2 mutations seems to be impaired dynein-mediated transport, the precise mechanism leading to the impairment differs depending on the protein domain and interacting molecules implicated. To date, a unifying pathomechanism for all mutations has not been elucidated.

Animal models

Three mouse models carrying heterozygous *Dync1h1* mutations mimic the phenotypes observed in humans. The *Dync1h1*^{Loa} (legs at odd angles) and *Dync1h1*^{Cra1} (cramping 1) mouse models, carrying a p.F580Y and p.Y1055C missense mutation in the DYNC1H1 tail domain, respectively, show progressive motor neuron degeneration (Hafezparast *et al.*, 2003). *Dync1h1*^{Swl} (sprawling) mice with a p.G1040_T1043delinsA mutation in the DYNC1H1 tail region display an early-onset proprioceptive sensory neuropathy (Chen *et al.*, 2007).

In *Drosophila*, loss of BicD leads to a strongly reduced rate of larval locomotion and lethality (Li *et al.*, 2010). Furthermore, transgenic mice with neuron-specific expression of the BICD2 N-terminus have impaired dynein/dynactin function and develop ALS-like features in motor neurons (Teuling *et al.*, 2008).

Lethal infantile spinal muscular atrophies with arthrogryposis

Major signs and symptoms

Lethal arthrogryposis with anterior horn cell disease and X-linked spinal muscular atrophy (SMAX2) are among the most severe forms of motor neuron disease (Greenberg *et al.*, 1988; Kobayashi *et al.*, 1995; Vuopala *et al.*, 1995; Nousiainen *et al.*, 2008; Ramser *et al.*, 2008). The clinical phenotype includes foetal immobility, hydrops, micrognatia, pulmonary hypoplasia, pterygia and multiple joint contractures, prenatal akinesia, arthrogryposis, hypotonia, areflexia, chest deformities, facial dysmorphism, bone fractures, and genital abnormalities. Death occurs in the early neonatal period as a result of respiratory failure. Electromyography and muscle biopsy findings are consistent with loss of anterior horn cells. Neuropathological findings include lack of anterior horn motor neurons, severe atrophy of the ventral spinal cord and hypoplastic, almost absent, skeletal muscles. There is a marked phenotypic overlap between lethal arthrogryposis with anterior horn cell disease and lethal congenital contracture syndrome.

Causative genes

Lethal arthrogryposis with anterior horn cell disease is an autosomal recessive condition caused by alterations in GLE1. All patients described to date carry compound heterozygous *GLE1* mutations, and many have one copy of the Fin$_{Major}$ allele (Nousiainen *et al.*, 2008). Fin$_{Major}$ is an intronic c.432-10A>G substitution, 10 nucleotides upstream of *GLE1* exon 4, with a high prevalence in Finnish patients. It creates a cryptic splice acceptor site, resulting in the insertion of three amino acids in the coiled-coil protein domain (p.T144_E145insPFQ).

SMAX2 is an X-linked recessive disorder caused by point mutations within exon 15 of the gene encoding ubiquitin-like modifier-activating enzyme 1 (*UBA1*) (Ramser *et al.*, 2008; Dlamini *et al.*, 2013). Apart from three missense mutations, one synonymous mutation (p.N577=) was identified, leading to a significant reduction of messenger RNA expression in patients' lymphocytes. The p.N577= transition underlying these expression changes is located within a CpG island, alters the DNA methylation pattern, and could as such play a role in *UBA1* expression (Dressman *et al.*, 2007).

Allelic disorders

Analysis of a large cohort of Finnish patients revealed that lethal arthrogryposis with anterior horn cell disease and lethal congenital contracture syndrome are allelic disorders, both caused by recessive mutations in *GLE1* (Nousiainen *et al.*, 2008). Almost all patients with lethal congenital contracture syndrome carry homozygous copies of the Fin$_{Major}$ allele. Furthermore, a dominant missense mutation in *GLE1* (p.R584W) is associated with dorsalization of the hands and feet by an unknown pathomechanism (Al-Qattan *et al.*, 2012).

Functional studies into the disease mechanism

GLE1 encodes a nucleoporin required for messenger RNA export from the nucleus to the cytoplasm, which self-associates via its coiled-coil domain (Folkmann *et al.*, 2013). Wild-type GLE1 oligomers form disk-shaped particles, whereas GLE1-Fin$_{Major}$ particles are disordered and malformed. Moreover, the Fin$_{Major}$ protein is defective in messenger RNA export, through the dysregulation of messenger RNA remodelling, and has slow nucleocytoplasmic shuttling. Thus, disease pathology could result from a loss-of-function mechanism, due to perturbations in GLE1 oligomerization or disrupted nuclear export of messenger RNA at nuclear pore complexes.

UBA1 (previously UBE1) is an E1 enzyme that initiates the activation and conjugation of ubiquitin-like proteins. The frequently mutated exon 15 encodes a highly conserved protein domain that interacts with gigaxonin (GAN), and is important for axonal structure and neuronal maintenance (Allen *et al*., 2005). By forming complexes with UBA1, GAN controls the degradation of ubiquitin-mediated microtubule-associated protein 1B (MAP1B). MAP1B has a role in neurodevelopment and neurodegeneration (Gomi and Uchida, 2012; Tymanskyj *et al*., 2012), and its over-expression in cortical neurons leads to cell death (Allen *et al*., 2005). Thus, missense mutations in the UBA1 interaction domain may lead to disturbances in the forming of complexes with GAN, with diminished MAP1B degradation, ultimately resulting in compromised neuronal survival. Furthermore, UBA1 physically interacts with SMN1 in neurons, and UBA1 levels are reduced in 5q SMA mouse models (Wishart *et al*., 2014). These results implicate ubiquitin-dependent pathways in SMA pathology, and provide a potential link between 5q and non-5q SMA forms.

Additionally, the ubiquitous export factor GLE1 may have tissue-specific effects contributing to the phenotype caused by the dominant p.R584W mutation; for instance, if it only affects the transport of a specific subset of messenger RNAs or if particular tissues are more sensitive to the temporospatial regulation of gene expression (Hurt and Silver, 2008).

Animal model

A zebrafish *GLE1* depletion model mimics the phenotype observed in human lethal congenital contracture syndrome 1 foetuses, including motor neuron deficiency resulting from apoptosis of neuronal precursors (Jao *et al*., 2012).

In *Drosophila*, loss-of-function mutations in *Uba1* reduce lifespan and result in severe motor impairment, recapitulating some aspects of human SMAX2 (Liu and Pfleger, 2013).

Spinal muscular atrophy with progressive myoclonic epilepsy

Major signs and symptoms

Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is an early-onset disorder (3–5 years of age), characterized by progressive muscle weakness of lower and upper limbs due to lower motor neuron damage (Haliloglu *et al*., 2002; Zhou *et al*., 2012). Myoclonic epilepsy, generally resistant to conventional therapy, is observed later in the disease course. As the disease progresses, it leads to dysphagia, respiratory muscle involvement, recurrent lung infections and severe disability or death before 20 years of age (Zhou *et al*., 2012).

Causative gene

SMA-PME is an autosomal recessive condition caused by mutations in the gene encoding N-acylsphingosine amidohydrolase (*ASAH1*) (Zhou *et al*., 2012). A missense mutation (p.T42M) is homozygous in two families and in a third family it is compound heterozygous with a whole-gene deletion.

Allelic disorder

Mutations in *ASAH1* are also associated with Farber lipogranulomatosis, a severe early-onset condition affecting multiple tissues (Koch *et al*., 1996).

Functional studies into the disease mechanism

ASAH1 is a lysosomal enzyme that degrades ceramide into sphingosine and free fatty acids. The p.T42M missense mutation does not influence transcript or protein expression, but acid-ceramidase activity is reduced to ~30%, hinting at a loss-of-enzymatic-function mechanism (Zhou *et al*., 2012). Patients with Farber disease exhibit even lower acid-ceramidase activity (<10%) (Levade *et al*., 2009). It is proposed that the higher residual enzymatic activity in patients with SMA-PME is responsible for the later-onset phenotype, restricted to spinal motor neurons and other areas of the CNS, as compared to the multisystemic, early-onset Farber disease.

Animal model

Asah1 knockdown in zebrafish embryos leads to defective motor neurons, with a marked loss of axonal branching and increased apoptosis in the spinal cord (Zhou *et al*., 2012).

Pontocerebellar hypoplasia with infantile spinal muscular atrophy

Major signs and symptoms

Pontocerebellar hypoplasia refers to a group of severe neurodegenerative disorders affecting the development and function of the brainstem and cerebellum (Chou *et al*., 1990; Barth, 1993; Rudnik-Schöneborn *et al*., 2003). Pontocerebellar hypoplasia type 1 is characterized by severe central and peripheral motor dysfunction, associated with anterior horn cell degeneration and death in early childhood due to respiratory insufficiency (Rudnik-Schöneborn *et al*., 2003; Salman *et al*., 2003; Renbaum *et al*., 2009). The disorder presents with psychomotor delay, microcephaly, severe hypotonia, tendon areflexia, and truncal and limb muscle weakness. Joint contractures and, in the case of prenatal onset, arthrogryposis, are also reported. EMG is neurogenic without sensory involvement. Muscle specimen shows neurogenic atrophy, and sural nerve biopsy proves axonopathy. Post-mortem assessments show anterior horn cell degeneration of the spinal cord and marked loss of Purkinje and granular cells with gliosis in the cerebellum.

Causative genes

Pontocerebellar hypoplasia type 1A is an autosomal recessive condition caused by mutations in vaccinia-related kinase 1 (*VRK1*) (Renbaum *et al*., 2009; Najmabadi *et al*., 2011). To date, two homozygous VRK1 mutations have been identified in consanguineous families: a nonsense mutation (p.R358X) causing significant reduction of messenger RNA levels due to nonsense-mediated messenger RNA decay, and a missense mutation (p.R133C).

Pontocerebellar hypoplasia type 1B is due to homozygous or compound heterozygous defects in the gene encoding exosome component 3 (*EXOSC3*) (Wan *et al*., 2012). *EXOSC3* mutations account for 37–75% of pontocerebellar hypoplasia type 1 families (Rudnik-Schöneborn *et al*., 2013; Eggens *et al*., 2014). With a prevalence of 55%, the most common mutation in all ethnic groups is the ancestral p.D132A mutation (Wan *et al*., 2012; Rudnik-Schöneborn *et al*., 2013). Among the additional mutations, several are predicted to result in null-alleles; for example, frameshift mutations, a mis-start mutation, a nonsense mutation and a partial gene deletion (Rudnik-Schöneborn *et al.*, 2013; Eggens *et al.*, 2014).

Allelic disorder

Recently, compound heterozygous *VRK1* mutations (p.V236M and p.R89Q) were found to cause HMSN plus microcephaly in two affected siblings (Gonzaga-Jauregui *et al.*, 2013). Notably, in an unrelated Ashkenazi-Jewish patient with a similar phenotype, the authors found the p.R358X mutation originally associated with pontocerebellar hypoplasia type 1A. Haplotype analysis revealed a founder effect (Gonzaga-Jauregui *et al.*, 2013). Although some clinical features of both families overlap (microcephaly, peripheral neuropathy with secondary muscle atrophy), several others are remarkably different (no pontocerebellar hypoplasia on MRI, no CNS neurological symptoms, and normal cognitive function in the HMSN family). How the same mutation can lead to different phenotypes in different families remains to be elucidated. A possible explanation could be differences in the degree of nonsense-mediated messenger RNA decay activity.

Functional studies into the disease mechanism

VRK1 is a serine/threonine kinase that phosphorylates p53 (TP53) and CREB1 and is essential for nuclear envelope formation, but its role in spinal motor neuron function is currently unexplored.

EXOSC3 forms an essential part of the human RNA exosome complex, the major cellular machinery for processing, surveillance and turnover of a diverse spectrum of coding and non-coding RNA species (Jensen, 2010). Due to its crucial function, complete loss of EXOSC3 is likely to be lethal. This is corroborated by the fact that predicted null-alleles (e.g. frameshift and splicing mutations) are always compound heterozygous with a missense mutation, which is supposed to retain some residual activity.

Animal model

Knockdown of endogenous *exosc3* expression in zebrafish embryos leads to a dose-dependent phenotype of a short, curved spine and small brain with poor motility and death within 3 days post-fertilization (Wan *et al.*, 2012). Co-injection with wild-type zebrafish or human *EXOSC3* messenger RNA can completely or partially rescue the abnormal phenotype, whereas rescue with zebrafish or human messenger RNA containing the mutations is ineffective. This suggests that the mutations disrupt normal EXOSC3 function, consistent with a loss-of-function mechanism.

Brown-Vialetto-Van Laere syndrome

Major signs and symptoms

Brown-Vialetto-Van Laere syndrome is a rare disorder, with a variable onset age (from infancy to early in the third decade), encompassing sensorineural deafness, bulbar palsy and respiratory compromise, often causing death (Sathasivam, 2008; Green *et al.*, 2010; Bosch *et al.*, 2012; Haack *et al.*, 2012; Johnson *et al.*, 2012; Toopchizadeh *et al.*, 2013). The early-onset cases tend to have a more rapid progression (Green *et al.*, 2010), although early motor milestones are usually normal (Bosch *et al.*, 2012). The course is invariably progressive, with involvement of lower motor neuron and lower cranial nerve (III–VI) palsies. Additional features include cerebellar ataxia, sensory neuropathy, optic atrophy, retinitis pigmentosa, mental retardation, and psychiatric abnormalities (Haack *et al.*, 2012).

Causative genes

Brown-Vialetto-Van Laere syndrome type 1 is an autosomal recessive condition caused by mutations in solute carrier family 52, riboflavin transporter, member 3 (*SLC52A3*, previously *RFT2*) (Green *et al.*, 2010). Multiple molecular defects have been identified, including nonsense, frameshift and missense mutations.

Brown-Vialetto-Van Laere syndrome type 2 is related to homozygous or compound heterozygous mutations in another riboflavin transporter gene, *SLC52A2* (previously *RFT3*) (Johnson *et al.*, 2012).

Allelic disorder

Fazio-Londe syndrome is considered the same disease entity as Brown-Vialetto-Van Laere syndrome, but it does not involve hearing loss (Dipti *et al.*, 2005).

Functional studies into the disease mechanism

SLC52A3 is a transmembrane protein that mediates the uptake of riboflavin, an essential vitamin (B2) that mainly functions in intermediate energy metabolism (Koy *et al.*, 2012). Riboflavin deficiency can lead to oxidative stress, and has been implicated in apoptotic pathways (Koy *et al.*, 2012). Patients with Brown-Vialetto-Van Laere syndrome type 1 have decreased plasma levels of riboflavin and its coenzyme forms (Bosch *et al.*, 2011). Furthermore, immunohistochemical characterization of SLC52A3 expression in patients with Brown-Vialetto-Van Laere syndrome type 1 shows a dramatically reduced punctate axonal staining (Malafronte *et al.*, 2013). Oral supplementation of riboflavin provides a life-saving treatment for young patients (Bosch *et al.*, 2011, 2012; Anand *et al.*, 2012; Ciccolella *et al.*, 2012; Koy *et al.*, 2012; Spagnoli *et al.*, 2014).

SLC52A2 alterations cause reduced riboflavin uptake and diminished protein expression (Foley *et al.*, 2014). In contrast to Brown-Vialetto-Van Laere syndrome type 1, however, patients with Brown-Vialetto-Van Laere syndrome type 2 do not show reduced plasma riboflavin levels. This is in line with the postulated function of SLC52A2 in riboflavin uptake from blood to target cells, rather than from food, as is the case for SLC52A3. Nevertheless, patients with Brown-Vialetto-Van Laere syndrome type 2 are also responsive to high-dose oral riboflavin treatment (Haack *et al.*, 2012; Johnson *et al.*, 2012; Foley *et al.*, 2014).

Late-onset conditions

Late-onset pure spinal muscular atrophy

Major signs and symptoms

Late-onset pure SMA is characterized by a clinical onset between the third and fifth decade, progressive proximal muscle weakness and atrophy, muscle cramps, fasciculations, and absent deep-tendon reflexes (Finkel, 1962; Jokela *et al.*, 2011; Rattay *et al.*, 2013). In an advanced stage, distal impairment may become apparent, but respiratory, bulbar, and facial muscles are spared. Affected individuals mostly remain ambulatory. EMG shows mild to moderate, widespread chronic and active neurogenic changes. Neurogenic changes are also observed in muscle biopsies from affected individuals.

Causative genes

Thus far, late-onset pure SMA has been associated with three separate loci. First, Finkel type SMA (SMA-FK) is an autosomal dominant condition caused by a dominant founder mutation (p.P56S) in the *VAPB* gene, encoding VAMP (vesicle-associated membrane protein)-associated protein B and C (Nishimura *et al.*, 2004). The mutation has a high prevalence in Brazil and, to date, ~200 cases have been described (Kosac *et al.*, 2013).

Second, in an isolated patient with adult-onset pure SMA, compound heterozygous mutations were identified in the gene encoding the beta-subunit of hexosaminidase (*HEXB*) (Rattay *et al.*, 2013). The patient carried one missense mutation (p.417L) that was previously described in patients with juvenile Sandhoff disease, and one novel macro-deletion of exons 1–5.

Third, Jokela type SMA (SMA-J) is an autosomal dominant form, significantly linked to an unsolved locus on chr22q in Finnish and Swedish patients with SMA (Jokela *et al.*, 2011; Penttila *et al.*, 2012). Sanger sequencing of the two best positional candidate genes (*SNRPD3* and *SGSM1*) showed no pathogenic mutations (Penttila *et al.*, 2014).

Allelic disorders

VAPB mutations, even the SMA-FK-associated p.P56S mutation, also cause other motor neuron phenotypes, particularly typical and atypical ALS (Nishimura *et al.*, 2005; Chen *et al.*, 2010; Funke *et al.*, 2010; Kosac *et al.*, 2013).

HEXB is a long-established causative gene for Sandhoff disease, a severe, progressive neurodegenerative disorder characterized by neuronal accumulation of gangliosides (Bikker *et al.*, 1989).

Functional studies into the disease mechanism

VAPB is a member of the vesicle-associated membrane protein (VAMP)-associated protein family that participates in the unfolded protein response (Kanekura *et al.*, 2006). *In vitro* expression studies have demonstrated that p.P56S dramatically disturbs VAPB subcellular distribution, causes numerous intracellular aggregates, and has a dominant-negative effect (Nishimura *et al.*, 2004; Teuling *et al.*, 2007). Furthermore, the mutant protein has an increased interaction with the outer mitochondrial membrane protein RMDN3 (previously known as PTPIP51), resulting in VAPB accumulation at mitochondria-associated membranes in the endoplasmic reticulum and elevated mitochondrial calcium uptake (De Vos *et al.*, 2012). These enhanced calcium levels disrupt anterograde axonal transport of mitochondria by affecting the outer mitochondrial membrane protein RHOT1 (previously known as MIRO1) and consequently kinesin 1 function (Morotz *et al.*, 2012).

HEXB encodes an enzyme involved in ganglioside breakdown. Mutations in *HEXB* result in the accumulation of non-degraded substrates in neuronal lysosomes, causing severe neurological dysfunction.

Animal models

In *Drosophila*, neuronal expression of p.P58S-altered VAP-33A (the fly homologue of VAPB) results in an increased bouton size at the neuromuscular junction and microtubule disorganization, and suggests a dominant-negative effect (Ratnaparkhi *et al.*, 2008). Moreover, it recapitulates major disease hallmarks, including locomotion defects, neuronal death and aggregate formation (Chai *et al.*, 2008). Transgenic mice with pan-neuronal expression of p.P56S VAPB develop progressive hyperactivity, deficit in motor coordination and balance, and gait abnormalities (Aliaga *et al.*, 2013). The mutant VAPB forms neuronal inclusions that represent a reversible endoplasmic reticulum quality-control compartment to isolate the misfolded protein (Kuijpers *et al.*, 2013). *Vapb* knockout leads to mild motor defects in mice and causes swimming deficits in zebrafish (Kabashi *et al.*, 2013).

Homozygous *Hexb* knockout mice show a progressive deterioration in motor function, swiftly evolving into an almost complete absence of movement (Sango *et al.*, 1995).

Spinal muscular atrophy with brisk tendon reflexes

Major signs and symptoms

Clinical onset varies between 10 and 35 years, with initial proximal, followed by distal muscle weakness in all four limbs, hand tremor and brisk tendon reflexes with no other signs of upper motor neuron involvement (Rudnik-Schöneborn *et al.*, 2012). The disease is slowly progressive. EMG is compatible with SMA.

Causative gene

Senataxin (*SETX*), a known ALS gene (Chen *et al.*, 2004), was identified in a dominant SMA family with retained tendon reflexes (Rudnik-Schöneborn *et al.*, 2012). The affected individuals carry a heterozygous missense variant (p.L389S), previously reported for ALS. Interestingly, the two affected siblings with an earlier onset age and more pronounced weakness have a second *SETX* mutation (p.V891A) of unknown pathogenicity in *trans*.

Allelic disorders

SETX is a known causative gene for childhood- and adolescent-onset forms of familial ALS, known as autosomal dominant juvenile ALS4 (Chen *et al.*, 2004). Furthermore, *SETX* is associated with autosomal recessive spinocerebellar ataxia (SCAR1) (Moreira *et al.*, 2004).

Functional studies into the disease mechanism

SETX is a helicase involved in the DNA damage response by repairing double-stranded breaks generated by oxidative stress (Suraweera *et al.*, 2007). The disease mechanism is currently unknown, although dysfunction of helicase activity or other steps in RNA processing are postulated (Chen *et al.*, 2004). This hypothesis is supported by the homology of *SETX* to the DNA/RNA helicase immunoglobulin mu-binding protein 2 (*IGHMBP2*), a causative gene for autosomal recessive distal SMA with respiratory distress (SMARD1) (Grohmann *et al*., 2001).

Adult-onset proximal spinal muscular atrophy followed by cardiac involvement

Major signs and symptoms

The phenotype is characterized by late onset (fourth to fifth decade), slowly progressive, predominantly proximal muscle weakness and atrophy, and cardiomyopathy in a later stage. Muscle biopsies display neurogenic features (Rudnik-Schöneborn *et al*., 2007).

Causative gene

Adult-onset SMA followed by cardiac involvement is a dominant disorder caused by two mutations in prelamin-A/C (*LMNA*) (Rudnik-Schöneborn *et al*., 2007). One is a nonsense mutation (p.Q493*) and the other a missense mutation (p.R377H), previously described in patients with limb-girdle muscular dystrophy type 1B (Muchir *et al*., 2000).

Allelic disorders

Laminopathies encompass an extremely broad range of disorders, categorized into two classes based on organ-system involvement: (i) myopathies, neuropathies and cardiopathies; and (ii) partial lipodystrophy, progeria syndromes and mandibuloacral dysplasia (Hegele, 2005). No clear-cut genotype–phenotype correlations can be defined, as the same mutation can cause distinct phenotypes, and mutations are scattered throughout the gene (Novelli and D'Apice, 2003).

Functional studies into the disease mechanism

LMNA encodes both lamin A and lamin C proteins that are structural components of the nuclear lamina. The p.Q493* mutated *LMNA* transcript could be subject to nonsense-mediated messenger RNA decay, but this has not yet been investigated. Other nonsense mutations in *LMNA* have been described for several laminopathy phenotypes (Novelli and D'Apice, 2003) and both haploinsufficiency and dominant negative effects have been proposed as disease mechanisms (Becane *et al*., 2000; Geiger *et al*., 2008). Furthermore, mutations introducing a premature stop codon may skew the lamin A to lamin C ratio, thus contributing to disease (Al-Saaidi *et al*., 2013). The p.R377H mutation is localized in the helical domain of the second coil and leads to mislocalization of both lamin and its interactor, emerin, in muscular and non-muscular cells (Charniot *et al*., 2003).

Thus far, the pathomechanism responsible for all of the different laminopathy phenotypes remains unclear. For class 1 laminopathies, such as SMA, proposed mechanisms include nuclear fragility, anomalous nuclear positioning, tissue-specific altered gene expression, and perturbation of the endoplasmic reticulum (Novelli and D'Apice, 2003). Lamin A/C deficiency is associated with both defective nuclear mechanics and impaired transcriptional activation (Lammerding *et al*., 2004). It causes loss of nuclear stiffness, and the loss of a physical interaction between nuclear lamins and the cytoskeleton may cause general cellular weakness (Broers *et al*., 2004).

Animal models

In mouse models of different laminopathies, an over-accumulation of the inner nuclear envelope SUN1 protein was found in the Golgi complex, as a result of reduced protein turnover (Chen *et al*., 2012). Loss of *Sun1* rescues the phenotype in mouse models, indicating that SUN1 accumulation is a common pathogenic event in laminopathies.

Okinawa type proximal hereditary motor and sensory neuropathy

Major signs and symptoms

Proximal hereditary motor and sensory neuropathy (HMSNP) is clinically characterized by young-adult onset and slowly progressive proximal muscle weakness and atrophy, muscle cramps, and fasciculations, with later onset of distal sensory impairment. The disease was first reported in Japanese patients, originating from Kansai and Okinawa, and afterwards in Korean and Brazilian patients of Japanese ancestry (Takashima *et al*., 1997; Maeda *et al*., 2007*a*,*b*; Patroclo *et al*., 2009; Ishiura *et al*., 2012; Lee *et al*., 2013). Nerve conduction studies and EMG show neurogenic changes and axonal motor and sensory polyneuropathy. Creatine phosphokinase is often increased.

Causative gene

Currently, one missense mutation (p.P285L) in the TRK-fused gene (*TFG*) has been found in five HMSNP families, displaying autosomal dominant inheritance (Ishiura *et al*., 2012; Lee *et al*., 2013). Detailed haplotype analysis suggests two independent origins of the mutation (Ishiura *et al*., 2012).

Allelic disorder

A homozygous missense mutation in VAPB causes hereditary spastic paraplegia 57 by impairing the structure of the endoplasmic reticulum (Beetz *et al*., 2013).

Functional studies into the disease mechanism

Neuropathological findings in patients' motor neurons include TFG- and ubiquitin-positive inclusion bodies, and fragmentation of the Golgi apparatus (Ishiura *et al*., 2012). Stable expression of mutant TFG in cultured neuronal cells results in mislocalization and TARDBP-positive inclusion body formation (Ishiura *et al*., 2012), whereas transient expression of mutant TFG does not show any alterations (Lee *et al*., 2013).

Kennedy disease, spinal and bulbar muscular atrophy

Major signs and symptoms

Kennedy disease is an X-linked recessive form of spinobulbar muscular atrophy usually starting in the third to fifth decade of life

(Sperfeld *et al.*, 2002; Echaniz-Laguna *et al.*, 2005). The disease predominantly affects males and is associated with progressive limb and bulbar weakness, chin and peri-oral fasciculations, and proximal and occasional distal muscle wasting (Kennedy *et al.*, 1968; Schoenen *et al.*, 1979; Harding *et al.*, 1982). Patients have variable involvement of the lower motor and sensory neurons, whereas upper motor neurons are spared. Motor nerve conduction studies are normal, but most patients have small or non-recordable sensory action potentials. Plasma creatine kinase levels are elevated in most cases. Muscle biopsies show neurogenic atrophy (Harding *et al.*, 1982). Patients with Kennedy disease may have endocrine manifestations, including diabetes mellitus, gynaecomastia, hyperlipoproteinaemia, hypobetalipoproteinaemia and reduced fertility (Wilde *et al.*, 1987; Nagashima *et al.*, 1988; Warner *et al.*, 1990; Sperfeld *et al.*, 2005).

Causative gene

Kennedy disease is caused by a CAG-repeat expansion in the first exon of the androgen receptor gene (*AR*). As the CAG-trinucleotide encodes a glutamine residue, SMAX1 belongs to the growing list of polyQ disorders associated with neurodegeneration. The CAG-repeat number ranges between 38 and 62 in patients, whereas unaffected individuals have 10–36 repeat copies. Repeat length correlates with disease severity (La Spada *et al.*, 1991; Doyu *et al.*, 1992).

Allelic disorder

AR is a causative gene for androgen insensitivity syndrome, an X-linked recessive disorder in which affected males have female external genitalia and breast development (Morris, 1953).

Functional studies into the disease mechanism

AR is a ligand-activated transcription factor. On androgen binding, AR exposes its nuclear localization signal and is directed to the nucleus, where it regulates gene expression and affects cellular differentiation and proliferation. The expanded polyQ-tract causes aggregation and proteolytic processing of the AR protein (Merry *et al.*, 1998). This accumulation of toxic AR protein species leads to motor neuron dysfunction and death, consistent with a gain-of-toxic function mechanism. The nucleus is believed to play a central role in disease, as this is where aberrantly cleaved polyQ-expanded AR inclusions are predominantly present. In transgenic mouse and cell models, abolishing the nuclear localization signal to sequester the toxic AR species in the cytoplasm is neuroprotective (Montie *et al.*, 2009).

Because Kennedy disease is an X-linked recessive trait, it affects males more than females. Females homozygously carrying the repeat expansion have only occasional muscle cramps and twitches (Schmidt *et al.*, 2002). It is suggested that the more pronounced disease manifestations in men are due to their higher levels of AR stimulation, which may result in an increased amount of abnormal transcription. This implies that blockage of AR might provide a therapeutic strategy to treat Kennedy disease.

Animal models

In *Drosophila*, over-expression of polyQ-expanded AR results in toxicity, with reduced larval locomotion and fewer boutons at the neuromuscular junction (Nedelsky *et al.*, 2010). Transgenic mice bearing a polyQ-expanded human AR reproduce many aspects of Kennedy disease, including slowly progressive, gender-specific motor deficits and neuronal intranuclear inclusions (Chevalier-Larsen *et al.*, 2004).

Pathomechanistic insights

Proximal non-5q spinal muscular atrophies are rare disorders that represent a diagnostic and management challenge for clinicians, researchers and patients. This heterogeneous group demonstrates clinical and genetic overlap with other neuromuscular disorders, such as HMSN, hereditary spastic paraplegia and ALS (Fig. 2). Moreover, the SMA-causing genes are mostly ubiquitously expressed and their molecular defects can affect other tissues, causing, for example, diverse laminopathies (*LMNA*), skeletal dysplasias (*TRPV4*), and malformations of cortical development (*DYNC1H1*).

The growing number of genes directly implicated in SMA is generating ever-expanding insights into the pathomechanisms leading to the disease. At present, no unifying disease mechanism has been identified, although, over the years, several common pathways have been found, including RNA metabolism or axonal transport. Here, we provide an unbiased overview of the molecular and cellular functions that are enriched among the 17 known proximal SMA-causing proteins, using a machine learning approach (Fig. 3). Details on the specific proteins assigned to each functional cluster are provided in Supplementary Table 1.

Perhaps unsurprisingly, the highest enrichment has been established for cellular death, survival and compromise. Indeed, many SMA genes encode proteins or enzymes essential for survival of the cell, or the motor neuron in particular (e.g. SMN1, DYNC1H1, LMNA, UBA1, etc.).

Molecular transport is another major function that is implicated, as many SMA genes encode trafficking proteins responsible for cation channelling (TRPV4), vitamin uptake (SLC52A3 and SLC52A2), hormone signalling (AR) and nuclear shuttling (LMNA, GLE1), among others.

Intriguingly, lipid metabolism also seems to be an important factor in SMA-related neuronal dysfunction. This is due to the involvement of enzymes such as ASAH1, which degrades ceramide into sphingosine and free fatty acids, and HEXB, which breaks down ganglioside, but also due to molecular motors (DYNC1H1, BICD2) transporting lipid droplets (Larsen *et al.*, 2008), and finally LMNA, where lipid accumulation is observed in class 2 laminopathy patients. Alterations in lipid metabolism are becoming an increasingly common theme in neuromuscular disorders. Defects in the breakdown of complex lipids have been implicated in several forms of hereditary spastic paraplegia (Rainier *et al.*, 2008; Tsaousidou *et al.*, 2008; Dick *et al.*, 2010; Schuurs-Hoeijmakers *et al.*, 2012; Tesson *et al.*, 2012; Boukhris *et al.*, 2013; Martin *et al.*, 2013). Additionally, hypolipidaemia was found at the presymptomatic stage in an ALS mouse model, suggesting an association with the disease mechanism (Kim *et al.*, 2011).

Another enriched function associated with SMA pathogenesis is RNA processing and trafficking, suggested by causative SMA

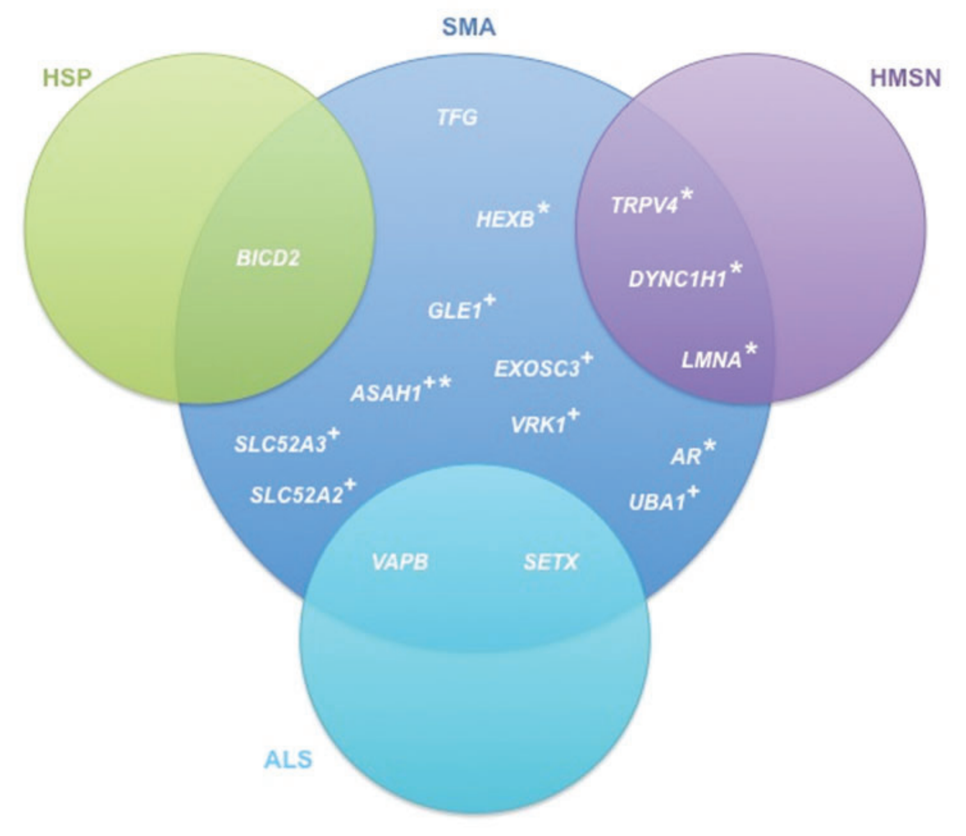

Figure 2 Clinical overlap of causal genes for SMA with other neuromuscular disorders. HSP = hereditary spastic paraplegia. Asterisks indicate genes that are also associated with non-neuromuscular diseases. Plus symbols indicate genes causing SMA with additional features, such as epilepsy or arthrogryposis.

genes such as EXOSC3, SETX and GLE1. Furthermore, the dynein molecular motor and its adaptor BICD2 could also be involved in messenger RNA transport (Swan and Suter, 1996).

Towards a cure

Identification of the causal gene, the type of genetic defect and the pathomechanism triggered is a crucial step towards a potential cure. A direct link between gene identification and therapy was recently illustrated in patients with Brown-Vialetto-Van Laere syndrome, who were found to have defects in riboflavin transporters. Simply supplementing riboflavin in the diet makes the difference between life and death in these patients, and causes drastic clinical improvement (Bosch *et al.*, 2012). In patients with Kennedy disease, knowledge about the nature of the defective gene prompted randomized placebo-controlled trials of androgen reduction therapy (Banno *et al.*, 2009; Katsuno *et al.*, 2010; Fernandez-Rhodes *et al.*, 2011). Despite the efficacy of this treatment in mouse models (Katsuno *et al.*, 2002; Chevalier-Larsen *et al.*, 2004), thus far clinical trials in human patients have not shown significant benefits. This might be due to their small scale or short duration, or because the initial testosterone levels of the patients treated were too low. More problematic is the speculation that androgen reduction might deprive patients of the anabolic benefits of endogenous androgens on the muscle. In future, therapies that alter the processing and degradation of mutated AR protein might provide a better alternative (Fischbeck, 2012). Overall, despite small successes in the treatment of a few specific forms, SMA remains an incurable disorder.

The road ahead

While only two decades ago non-5q SMA was an almost anecdotal diagnosis, today a growing number of conditions are assigned to this clinical category. The recent rise in the discovery rate of non-5q clinical and genetic entities is primarily due to progress in next generation sequencing technology development (Fig. 4). Of the 17 known SMA genes, six were identified through whole-exome sequencing (*DYNC1H1*, *TFG*, *ASAH1*, *EXOSC3*, *SLC52A2*, *BICD2*). This is equivalent to 60% of the novel SMA genes found since the advent of whole exome sequencing (Ng *et al.*, 2010). When omitting novel SMA genes previously linked with other neuromuscular diseases, the percentage of genes discovered with next generation sequencing rises to 86% (six of seven).

It is increasingly common to find SMA-causing mutations in genes previously associated with completely different types of pathology (e.g. the *TRPV4* allelic disorders). Phenotypic

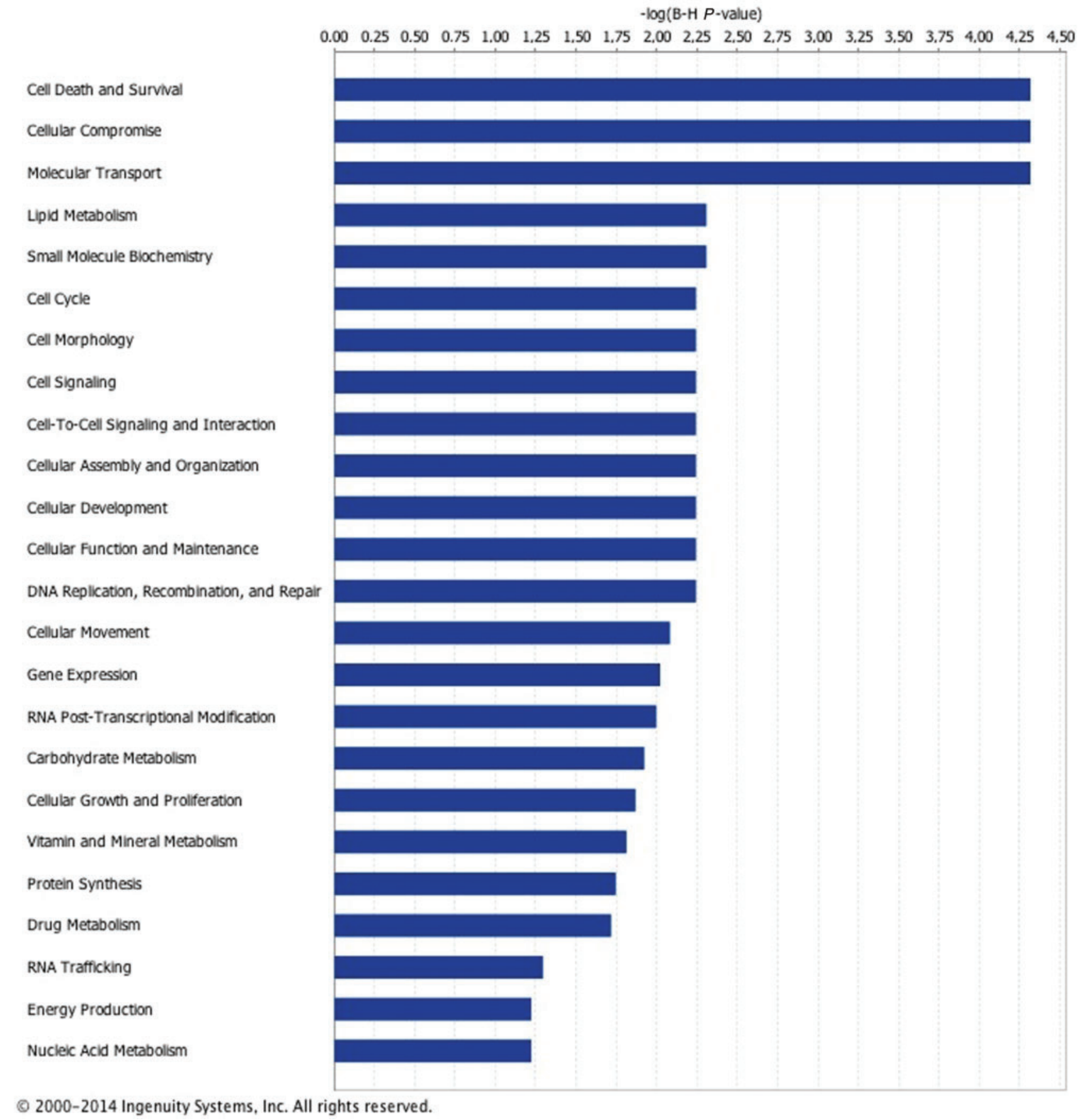

Figure 3 Enriched molecular and cellular functions associated with causal SMA genes. Ingenuity Pathway Analysis (IPA version 10830641) was used to summarize the molecular and cellular functions that were most strongly associated with genes linked to inherited SMAs. *P*-values were calculated using Fisher's exact test and corrected for multiple testing using the Benjamini-Hochberg method. As a cut-off for significance a *P*-value of 0.05 was used. The same gene can be present in multiple clusters.

differences can be partially attributable to the type of mutation; for example, a p.T42M missense mutation in ASAH1, retaining some residual activity, causes SMA-PME, whereas whole gene deletions, associated with total loss of protein function, result in severe Farber disease. Moreover, mutations may affect protein function in a cell-specific manner, possibly by interacting with regulatory proteins or complexes that are cell-type specific. Tissue-specific effects may also originate from differences in spatiotemporal gene expression. However, mutational differences alone cannot justify all phenotypic diversity, as precisely the same mutation may cause different disease manifestations even within the same family, for example, p.R315W in TRPV4 (Auer-Grumbach *et al.*, 2010). It is possible that other genetic or environmental factors might be at play, or the disease-causing protein

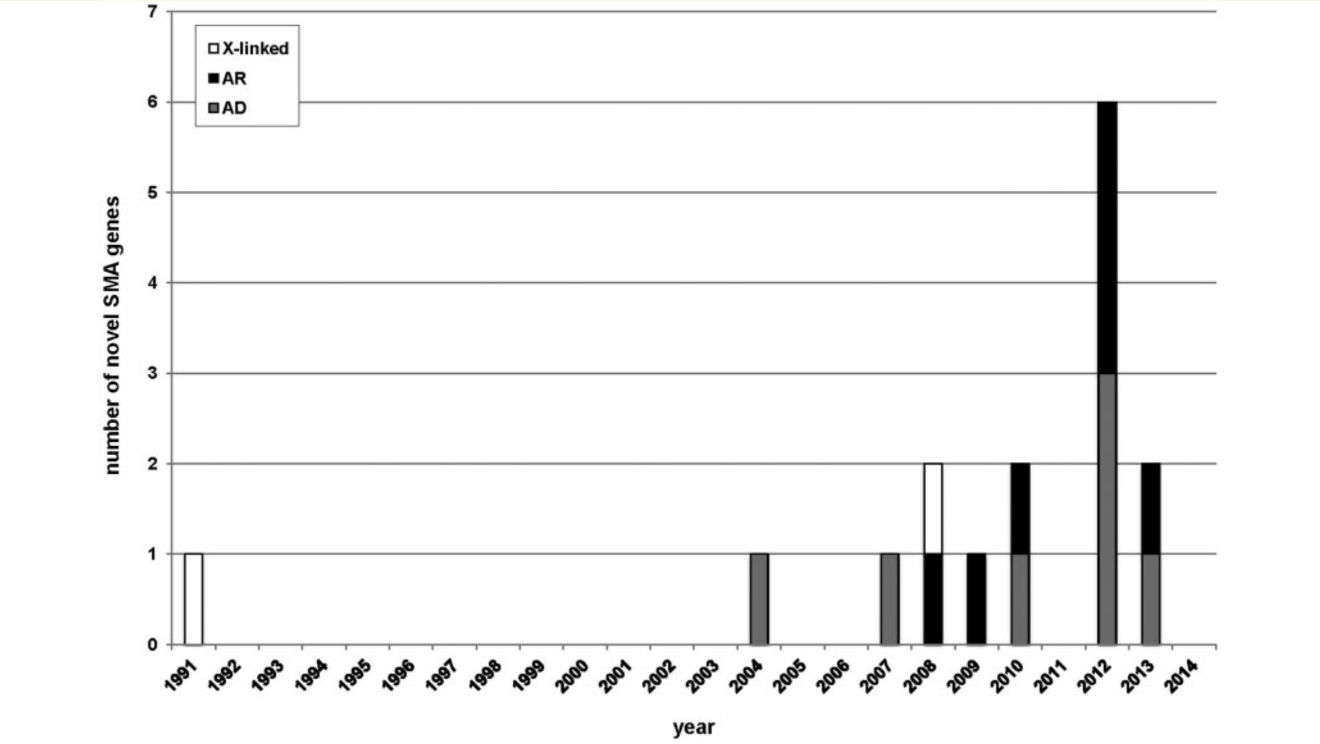

Figure 4 Timeline of discovery of genes involved in *SMN1*-negative SMA. Genes are classified based upon mode of inheritance [autosomal dominant (AD) in grey; autosomal recessive (AR) in black; X-linked in white]. The recent dramatic rise in the discovery rate is related to the advent of next generation sequencing technologies.

might gain unexplored alternative functions. At this point, however, we can only tentatively speculate about the putative mechanisms by which mutations in a single gene induce such a large variety of pathological phenotypes. Unravelling the aetiology of the different SMA forms will require an in-depth understanding of the role of the mutated proteins in complex cellular functions and constitutes a major goal of future research.

The phenotypic spectrum associated with many of the SMA genes is either too broad or not sufficiently known to pinpoint the relevant SMA subtype. Furthermore, clinical testing of individual genes is offered by only a handful of international laboratories dispersed throughout the world. The application of massive parallel sequencing technologies for the testing of multiple genes simultaneously would be an efficient approach to molecular diagnosis in a subset of patients. This would also aid in the classification of the different SMA forms based on the causal gene and help resolve the challenges in clinical phenotyping.

At the moment, next generation sequencing of customized gene panels has an important advantage over whole exome/genome sequencing for use in clinical practice, as it reaches sufficient read depth and sequencing coverage. The application of gene panels also poses fewer ethical issues, as it substantially reduces the chance of incidental findings. Due to the highly heterogeneous nature of non-5q SMA, however, the use of a gene panel for SMA is limited, because newly discovered genes would soon render the panel obsolete and it would require continuous updating. As the cost of whole-exome and whole-genome sequencing is dropping and the coverage improving, in future we foresee this as the preferred technology for diagnostics of known and novel disease genes. At present, however, the clinical application of this approach remains under debate (Rehm, 2013).

Furthermore, finding the one causal mutation is challenging considering the large number of genetic variations per individual. Therefore, it is not surprising that in the recent success stories presented by the authors and others, whole exome sequencing is combined with traditional mapping approaches to limit the number of candidate variations. Today families tend to be smaller and, due to the disease severity, many unsolved cases represent single patients. In such situations, it is impossible to apply positional cloning approaches such as linkage analysis or homozygosity mapping. Even so, establishing the probable mode of inheritance in a family significantly influences the diagnostic yield, as it determines the filtering strategy of next generation sequencing data (Sawyer *et al.*, 2014).

Clearly, the next major challenge will be to determine the pathogenicity of a multitude of potential mutations. For a rare disorder such as SMA, obtaining independent genetic evidence for pathogenicity, i.e. a second mutation in the same gene in an unrelated patient, is often difficult. Large-scale international collaborations that share findings from individual patients with similar phenotypes and the pooling of data in gene- and phenotype-specific databases would facilitate the diagnostic process. This approach was recently applied by research labs submitting data to the GEnomes Management Application (GEM.app) database, leading to the successful identification of genetic defects in *BICD2* as a cause of SMA and hereditary spastic paraplegia

(Oates *et al*., 2013). Furthermore, robust and high-throughput functional models to interpret the relevance of genetic variations are urgently needed. These translational tools could also facilitate the development of personalized medicines. Efforts are already being made to model potentially clinically significant variations (e.g. in zebrafish) (Niederriter *et al*., 2013). Ultimately, the mutations in newly identified genes will require iterative clinical examination to confirm the individual molecular diagnosis, especially in the case of allelic disorders.

Conclusions

In conclusion, non-5q SMA has long represented a challenge for clinicians and scientists due to its enormous variability, both clinically and genetically. The advances in next generation sequencing have elucidated the causal genes for many SMA types, yet this only further complicates matters by revealing overlaps with several other neuromuscular disorders. The proportion of patients with SMA for whom we can achieve a genetic diagnosis has dramatically increased in the past few years, and is expected to rise even more with the rapid advance of next generation sequencing technologies and lower costs. The major challenge for the future will be determining the pathogenicity of the causal mutation among a multitude of genetic alterations. To this end, platforms for sharing of next generation sequencing data should be developed to increase the chances of finding a second hit, and accurate and predictive models of SMA ought to be created for high-throughput screening of potential mutations and for the identification of drug hits. These are exciting times in the field of spinal muscular atrophies.

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Supplementary material

Supplementary material is available at *Brain* online.

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