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Review

Recent progress in the genetics of motor neuron disease

Josef Finsterer [a,*], Jean-Marc Burgunder [b]

[a] Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria
[b] Department of Neurology, University of Bern, Inselspital, CH-3010 Bern, Switzerland

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ABSTRACT

Background: Genetic background and pathogenesis of motor neuron diseases (MNDs) have been increasingly elucidated over recent years.
Aims: To give an overview about publications during the last year concerning the genetic background and phenotypic manifestations of MNDs, such as familial or sporadic amyotrophic lateral sclerosis (fALS, sALS), spinal muscular atrophies (SMA), bulbospinal muscular atrophy (BSMA), and unclassified MNDs.
Methods: Pubmed search for literature about ALS, SMA, and BSMA for the period 10/2012 to 9/2013.
Results: An increasing number of mutated genes is recognised in fALS but also sALS patients. Genes mutated in sALS include C9orf72, SOD1, TARDBP, FUS, UBQL2, SQSTM1, DCTN1, and UNC13A. Juvenile (onset <20 y) and adult ALS (early onset 20–60 y, late onset >60 y) are differentiated. Juvenile fALS is most frequently caused by mutations in ALS2, SETX, spatacsin, or Sigmar1 and adult fALS by mutations in C9orf72, SOD1, TARDBP, and FUS. Onset, phenotype, progression, and outcome of ALS are variable between different mutations, different genes, and different countries. Differentiation between sALS and fALS cases becomes artificial.
Conclusions: Further progress has been made over the last year in the clarification and understanding of the aetiology and pathogenesis of MNDs. However, further effort is needed to answer the many remaining questions.

1. Introduction

Motor neuron diseases (MNDs) are characterised by exclusive or predominant affection of the first (upper motor neuron (UMN)) or second motor neuron (lower motor neuron (LMN)) [Sabatelli et al., 2013]. In the majority of the cases, MNDs have a genetic cause and less frequently are acquired. Hereditary MNDs comprise sporadic and familial amyotrophic lateral sclerosis (sALS, fALS), spinal muscular atrophy (SMA), bulbospinal muscular atrophy (Kennedy syndrome), and some rare unclassified, hereditary MNDs. During recent years, an increasing number of mutated genes has been identified which cause fALS (Table 1) highlighting the genetic heterogeneity of these disorders, and the pathogenetic background of SMA and BSMA is more profoundly understood than before. This mini-review wants to give an overview about and discuss recent findings concerning the genetic background and phenotypic manifestations of ALS, SMA, BSMA, and the unclassified MNDs. Primary lateral slcerois and hereditary spastic paraplegias were not included since the review focuses on disorders with lower motor neuron involvement. Motor neuropathies were not included since they are not regarded as a neuronopathy.

2. Methods

Data for this review were identified by searches of MEDLINE, Current Contents, and PubMed, and references from relevant articles using the search terms “motor neuron desease”, “amyotrophic lateral sclerosis”, “spinal muscular atrophy”, “bulbospinal muscular atrophy” “gangliosidosis”, in combination with “genetics”, and “mutation”, Original papers but no abstracts or reports from meetings about randomized clinical trials, longitudinal studies, case series, and single cases were considered. Only articles published in English between October 2012 and September 2013 were included. Appropriate articles were studied and discussed for their suitability and reference lists of appropriate hits were studied for more appropriate papers. The review is divided into parts about ALS, SMA, BSMA, and unclassified MNDs.

3. Results

3.1. Amyotrophic lateral sclerosis (ALS)

ALS, the most common MND in adults [Ravits et al., 2013; Verma and Tandan, 2013] and the third most common adult-onset neurodegenerative disease, is a syndrome [Martin and Wong, 2013]. Half of the patients have cognitive impairment and of

* Corresponding author. Tel.: +43 1 71165 92085; fax: +43 1 4781711.
E-mail address: fifigs1@yahoo.de (J. Finsterer).

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Table 1
Mutated genes found in fALS or sALS cases.

Gene	Protein	Function	fALS	sALS	MOI	Phenotype plus/variant	Histology	References
SOD1	SOD	Enzyme, antioxidante	fALS1	Yes	AD/AR	No	Aggregates	Basso et al. [2013]; Tortelli et al. [2013]
Alsin	ALS2	TRAF, ESCRT	f + jALS2	No	AR	PLS, IAHSP	np	Chen et al. [2013]; Çobanoğlu et al. [2012]
SETX	Senataxin	Regulates replication	f + jALS4	No	AR	SCAR1, AOA2	np	Arning et al. [2013]
SPG11	Spatacsin	Unclear	f + jALS5	No	AR	No	np	Chen et al. [2013]; Orlacchio et al. [2010]
FUS/TLS	FUS	RBP	f + jALS6	Yes	AD/AR	FTLD	Aggregates	Daigle et al. [2013]; Niu et al. [2012]; Scaramuzzino et al. [2013]
VAPB	VAMP	ERGP, TRAF	fALS8	No	AD	SMA	TDP-43, VAMP	Kuijpers et al. [2013]; Qin et al. [2013]
ANG	Angiogenin	RBP, angiogenesis ↑	fALS9	Yes	AD	FTLD, EPD	np	Padhi et al. [2013]; Thiyagarajan et al. [2012]
TARDBP	TDP-43	RBP	fALS10	Yes	AD	FTLD	TDP-43	Armstrong and Drapeau [2013]; Tanaka et al. [2013]
FIG4	FIG4	PRD, ERGP, TRAF	fALS11	Yes	AD	CMT4J	np	Chen et al. [2013]; Iguchi et al. [2013]
OPTN	Optineurin	PRD, ERGP, TRAF	fALS12	Yes	AD/AR	EPD, FTLD, aphasia, OAG	TDP-43	Czell et al. [2013]; Kamada et al. [2013]; Weishaupt et al. [2013]
VCP	VCP	PRD	fALS14	No	AD	Paget, IBM, FTLD	TDP-43	González-Pérez et al. [2012]; Igari et al. [2013]
UBQLN2	Ubiquilin-2	PRD	f + jALS15	Yes	XR	FTLD	Aggregates	Gellera et al. [2013]
SigMAR1	Sigma recept.1	ERGP	f + jALS16	No	AR	FTLD	Aggregates	Prause et al. [2013]
PFN1	Profilin	Polymerises actin	fALS18	Yes	AD	FTLD	Aggregates	Daoud et al. [2013]; Ingre et al. [2013]; Tiloca et al. [2013]
ERBB4	ERBB4	TRAF	fALS19	No	AD	No	np	Takahashi et al. [2013]
C9orf72	Unknown	TRAF, repeats	fALS	Yes	AD	FTLD, EPD, psychosis	TDP-43. p62	Iguchi et al. [2013]; Williams et al. [2013]; Xu et al. [2013]
CHMP2B	Unknown	PRD, TRAF, ESCRT	fALS	Yes	AD	FTD	p38 MAPK ↓	Cox et al. [2010]; van Blitterswijk et al. [2012a,b]
DAO	D-AA oxidase	AA oxidation	fALS	No	AD	No	Aggregates	Iguchi et al. [2013]; Paul and de Belleroche [2012]
DCTN1	Dynactin	TRAF	fALS	Yes	AD	FTD	np	Iguchi et al. [2013]; Kuźma-Kozakiewicz et al. [2013]
SQSTM1	p62 protein	PRD	fALS	Yes	AD	Paget (bone)	TDP-43	Hirano et al. [2013]; Teyssou et al. [2013]
hnRNPA1	hnRNPA1	RBP	fALS	Yes	np	IBM, Paget, FTD	np	Calini et al. [2013]
Erlin2	Erlin	ER lipid rafts	jALS	Yes	No	No	np	Al-Saif et al. [2012]
UNC13A	UNC13	Controls transmitters	No	Yes	No	No	np	van Es et al. [2009]
NEFH	Neurofilament	TRAF	No	Yes	Ad	No	np	Figlewicz et al. [1994]
PRPH	Peripherin	TRAF	No	Yes	No	No	np	Corrado et al. [2011]
TAF15	TBP factor 15	RBP	No	Yes	AD	No	np	Iguchi et al. [2013]; Robberecht and Philips [2013]
GRN	Progranulin	Cell growth regulator	No	Yes	No	EPD, FTLD, aphasia	TDP-43	Cannon et al. [2013]
EWSR1	EWSR1	RBP	No	Yes	No	EPD, FTLD	np	Iguchi et al. [2013]; Robberecht and Philips [2013]
ATXN2	Ataxin-2	Repeat expansion	No	Yes	AD	SCA2	Aggregates	Iguchi et al. [2013]

MOI: mode if inheritance, TRAF: trafficking, ESCRT: endosomal sorting complexes required for transport, AA: aminoacid, PRD: protein degradation, ERGP: ER-Golgi pathway, jALS: juvenile ALS, FTLD: fronto-temporal lobe degeneration, RBP: RNA-binding protein, PLS: primary lateral sclerosis, IAHSP: infantile-onset ascending hereditary spastic paraplegia, SCAR1: autosomal recessive spinocerebellar ataxia, AOA: ataxia ocular apraxia, SMA: spinal muscular atrophy, and np: not provided.

these 15% meet the criteria for fronto-temporal dementia (FTD) [Vengoechea et al., 2013]. sALS is differentiated into sALS and fALS [Ravits et al., 2013] but only 5–10% of the ALS cases are familial (>1 affected patient in a family) [Tanaka et al., 2013; Vengoechea et al., 2013]. fALS is genotypically and phenotypically heterogeneous (Table 1) [Ravits et al., 2013] fALS follows an autosomal dominant, autosomal recessive, or X-chromosmal trait of inheritance. Mutations in genes associated with fALS have a number of different effects (Table 2) of which the most frequent is an increased propensity to produce misfolded and aggregated proteins [Trippier et al., 2012]. Additionally, ground-braking discoveries of mutations in genes encoding RNA-processing proteins and demonstration that abnormal aggregation of these and other proteins precede motor neuron loss in sALS and fALS have been recently made [Trippier et al., 2012; Verma and Tandan, 2013]. Some of these RNA-binding proteins have prion-like domains (PrWD, PrLD) with a propensity to self-aggregation (Table 1) [Kim et al., 2013; Verma and Tandan, 2013]. From these findings the hypothesis emerged that a focal cascade of toxic protein aggregates and their non-cell autonomous spread to neighbourhood groups of neurons (cell–cell interactions between neurons) could explain the temporo-spatial progression of ALS [Ravits et al., 2013; Verma and Tandan, 2013]. Mutant proteins in astrocytes may contribute to the pathogenesis of ALS [Kunze et al., 2013]. A key molecule associated with sALS and fALS is TDP-43, which is a pathological feature but can be mutated by itself as well [Iguchi et al., 2013].

Table 2
Pathogenetic mechanisms of mutated ALS genes [Robberecht and Philips, 2013].

Mechanism	Example
Enzyme defect	SOD1
RNA-binding ↑, impaired protein processing	TDP-43, FUS, ANG, SEXT, TAF15, EWSR1
Nucleotide expansion	C9orf72, ATXN2
Protein proteostasis	OPTN, UBQLN2, SQSTM1, VCP, CHMB2P, FIG4
Excitotoxicity	DAO
Defect cytoskeleton or cellular transport	VAPB, peripherin, DCTN1, NFH, PFN1
Unclear	Spatacsin, ALS2

3.1.1. sALS

sALS is diagnosed if there is UMN and LMN affection with or without cognitive impairment in a single member of a family. If more than one patient in a family is affected fALS is diagnosed. Meanwhile, it turned out that sALS can manifest clinically as a continuum between exclusive affection of the UMN or exclusive affection of the LMN. Exclusive affection of the LMN results in progressive muscular atrophy (PMA), predominant affection of the LMN with some UMN involvement in the classical Charcot-type of ALS, predominant affection of the UMN in the UMN-dominant type, and exclusive affection of the UMN in primary lateral sclerosis (PLS). Site of onset may be the limbs, bulbar muscles, proximal upper limbs (flail-arm syndrome), hemiparesis (Mill's hemiparetic type), or the respiratory muscles (in 5%). The concept of a pure motor condition, however, has to be abandoned given the increasing awareness that ALS may be associated with FTLD, FTD, psychiatric manifestations like psychosis or suicide, aphasia, or parkinsonism. Survival is on the average 3 y but ranges from a few months to >20 y. Old age, bulbar onset, and respiratory symptoms at onset are negative predictors for survival. Predictors for long survival are juvenile or early adult-onset, UMN-dominance, and flail-arm syndrome.

During recent years contribution of large- or low-effect genes to the pathogenesis of sALS is increasingly recognised (Table 2) [Sabatelli et al., 2013]. Among these are C9orf27, SOD1, FUS, TARDBP, UBQLN2, PFN1, DCTN1, hnRNPA1, SQSTN1, ANG, FIG4, OPTN1, CHMP2B, erlin2, UNC13A, NEFH, PRPH, TAF15, GRN, EWSR1, and ATXN2 (Table 1). Recently, sALS has been shown to be associated also with mutations in the chromatin remodelling complex component SS18L1 (CREST) gene [Chesi et al., 2013]. CREST mutations inhibit neurite outgrowth in primary neurons and the mutated protein associates with fused in sarcoma/translocated in liposarcoma (FUS/TLS) [Chesi et al., 2013]. Pathohistologically, sALS is characterised by ubiquitinated (ubiquitination is required prior to degradation of an abnormal protein) cytoplasmic inclusions of trans-activating response region DNA-binding protein (TDP-43), which can be also found in fronto-temporal lobe dysfunction (FTLD) [Arnold et al., 2013; Han et al., 2013; Ravits et al., 2013].

3.1.2. SOD1 (fALS1)

fALS1 is clinically characterised by a classical ALS phenotype [Chen et al., 2013]. Cognitive impairment is very rare and bulbar onset is less frequent than in other fALS types [Sabatelli et al., 2013]. Mean age at onset is later than in FUS patients but earlier than in other non-SOD1 patients [Sabatelli et al., 2013]. fALS1 follows an autosomal dominant (AD)/autosomal recessive (AR) trait of inheritance and is due to mutations in the SOD1 gene, encoding the Cu/Zn superoxide-dismutase [Chen et al., 2013]. More than 160 missense mutations are known to date [Tortelli et al., 2013]. Recently, new mutations have been detected by whole exome sequencing [Klein et al., 2013]. They cause fALS1 or sALS [Tortelli et al., 2013]. In a recent study on 60 Iranian patients the frequency of SOD1 mutations was 38.5% among fALS patients and 4.3% among sALS patients [Alavi et al., 2014]. Other studies showed that fALS is due to SOD1 mutations in about 20% of the cases [Tan et al., 2013]. Among fALS patients SOD1 is, after the S9orf72, the second most frequently mutated gene in ALS [Tortelli et al., 2013].

A pathomorphologic hallmark of SOD1-linked fALS is SOD1 immuno-positive inclusions found within motor neurons and the lack of classical ubiquitine or TDP43+ inclusions [Chen et al., 2013]. The mechanism, by which SOD1 becomes aggregated, however, still remains elusive [Chen et al., 2013]. Wild-type SOD1 forms a highly conserved intra-molecular disulphide bond whereas mutant SOD1 proteins are cross-linked via aberrant intermolecular disulphide cross-links [Toichi et al., 2013]. However, intermolecular disulphide bonding is not necessary for the formation of detergent-insoluble mutant SOD1 complexes [Roberts et al., 2012]. Misfolding can be explained by scrambling of a disulphide bond among four Cys residues in the structurally destabilised mutant SOD1 [Toichi et al., 2013]. Aggregation seems to be modulated by cysteine residues in mutant SOD1 [Roberts et al., 2012]. A contributing factor to accumulation of mutant SOD1 aggregates may be NO-mediated S-nitrosylation of the protein disulphide isomerase [Chen et al., 2013]. The degree of misfolded SOD1 is dependent on the location of the mutation [Ayers et al., 2013]. SOD1 is assumed to cause neurodegeneration by a novel cytotoxic activity of misfolded SOD1 affecting DNA/RNA metabolism, mitochondria, neurofilaments, axonal transport, the endoplasmatic reticulum, the Golgi apparatus, or the proteasome complex (involved in the protein quality control) [Sabatelli et al., 2013]. Mutant SOD1 modulates histone deacetylase-6 (HDAC6) activity and increases tubulin acetylation, which in turn facilitates mutant SOD1 aggregation [Gal et al., 2013]. The misfolded conformation of SOD1, shared by various ALS-linked SOD1 mutations but not by the wild-type protein, may promote neuroinflammation and can be detected by AJ10 antibodies [Sábado et al., 2013]. In mitochondria mitochondrial SOD1 forms a complex with Bcl-2, resulting in mitochondrial dysfunction [Tan et al., 2013]. Small SOD1-like peptides, which specifically block the formation of mtSOD1/Bcl-2 may recover mitochondrial dysfunction [Tan et al., 2013]. In a cell model of ALS oxidative stress was detrimental to oxygen consumption and glycolytic flux leading to a cellular energy deficit [Richardson et al., 2013]. Mutant SOD1 has also a substantial impact on protein secretion pathways in astrocytes, contributing to motor neuron degeneration [Basso et al., 2013].

3.1.3. ALS2 (fALS2)

Phenotypically, fALS2 is characterised by a slowly progressive lesion predominantly of the UMN manifesting as facial or limb spasticity [Chen et al., 2013]. fALS2 follows an AR trait of inheritance and is due to mutations in the ALS2 gene encoding for alsin [Chen et al., 2013]. ALS2 mutations may also manifest as primary lateral sclerosis (PLS) or infantile-onset ascending hereditary spastic paralysis (IAHSP) [Chen et al., 2013]. Alsin is related to spartin on the mRNA and protein level [Çobanoğlu et al., 2012]. Both proteins colocalise and the spartin isoform A precipitates with alsin in the same protein complex [Çobanoğlu et al., 2012].

3.1.4. SETX (fALS4)

Phenotypically, fALS4 presents with a slowly progressive, distal hereditary motor neuropathy with pyramidal signs [Chen et al., 2013]. fALS4 follows an AD trait of inheritance and is due to mutations in the SETX gene encoding for senataxin [Arning et al., 2013]. Mutations in the SETX gene may also cause AR spinocerebellar ataxia (SCAR1) or ataxia ocular apraxia-2 (AOA2) [Chen et al., 2013]. Recently, however, it has been shown that all newly identified variations are most likely non-pathogenic [Arning et al., 2013]. Attributing fALS4 to SETX mutations possibly resulted from interpretation of SEXT missense alleles in the absence of functional assays [Arning et al., 2013].

3.1.5. SPG11 (fALS5)

fALS5 is clinically characterised by a slowly progressive sometimes juvenile ALS phenotype [Chen et al., 2013]. Juvenile ALS is characterised by an onset <20 y of age, a positive family history in the majority of the cases, a mild course except for sporadic cases, and both an AD or AR trait of inheritance. fALS5 follows an AR mode of inheritance and is due to mutations in the SPG11 gene encoding spatacsin [Chen et al., 2013]. Mutations in SPG11 may also cause hereditary spastic paraplegia (HSP) [Chen et al., 2013]. Recently,

spatacsin mutations were found in 10 of 25 unrelated families with AR juvenile ALS [Orlacchio et al., 2010].

3.1.6. FUS (fALS6)

fALS6 is clinically characterised by a typical ALS phenotype [Chen et al., 2013]. It follows both an AD or AR mode of inheritance and is due to mutations in the FUS gene encoding the fused in sarcoma protein [Chen et al., 2013; Iguchi et al., 2013]. Mutations in FUS are clustered in the C-terminal nuclear localisation sequence (NLS) of the protein [Niu et al., 2012]. FUS is a DNA/RNA-binding protein (RBP) that forms cytoplasmic aggregates [Daigle et al., 2013] Classical ubiquitine or TDP43+ inclusions are lacking. Recently, it has been shown that mutations in FUS not only cause classical ALS but also FTLD [Scaramuzzino et al., 2013]. FUS mutations are responsible for fALS as well as sALS [Farg et al., 2013]. The FUS protein is imported into the nucleus by transportin (Trn1) [Niu et al., 2012]. ALS mutants cause decreased affinity of FUS with transportin [Niu et al., 2012]. In patients with fALS6, FUS is redistributed from the nucleus to the cytoplasm, where it triggers endoplasmatic reticulum stress [Farg et al., 2013]. FUS mutations cause fragmentation of the Golgi apparatus [Farg et al., 2013]. A potent modifier of the FUS pathology is an intermediate repeat length in the ataxin-2 (ATXN2) gene. A repeat number of 27–33 increases the risk of ALS [Farg et al., 2013]. In case ataxin-2 Q31 is co-expressed with mutant FUS, Golgi-fragmentation is enhanced and apoptosis triggered [Farg et al., 2013]. If the RNA-binding sites are abolished by mutations to produce an RNA-binding deficit, FUS exclusively localises to the nucleus but if the RNA-binding ability of FUS is preserved, FUS is incorporated into cytoplasmatic stress granules [Daigle et al., 2013]. The RNA-binding ability thus seems to be essential for the neurodegenerative phenotype of mutant FUS [Daigle et al., 2013]. Posttranslational arginine-methylation of FUS may contribute to the pathogenesis of FUS mutations in fALS6 [Scaramuzzino et al., 2013].

3.1.7. VAPB (fALS8)

fALS8 is clinically characterised by a typical or atypical ALS phenotype [Chen et al., 2013]. fALS8 follows an AD trait of inheritance and is due to mutations in the VAPB gene encoding the vesicle associated membrane protein associated protein-B (VAPB) [Chen et al., 2013; Qin et al., 2013; Kuijpers et al., 2013]. VAPB is an integral membrane protein of the endoplasmatic reticulum and a binding partner of YIF1A [Kuijpers et al., 2013]. In addition to fALS8, VAPB mutations may also cause spinal muscular atrophy (SMA) [Chen et al., 2013]. fALS8 is characterised by severe aggregation of the mutated protein [Qin et al., 2013].

3.1.8. ANG (fALS9)

fALS9 is phenotypically characterised by typical ALS, FTLD, and parkinsonism [Chen et al., 2013; Thiyagarajan et al., 2012]. fALS9 follows an AD mode of inheritance and is due to mutations in the ANG gene encoding angiogenin, a member of the ribonuclease-A superfamily [Chen et al., 2013; Padhi et al., 2013; Thiyagarajan et al., 2012]. Angiogenin has both neurotrophic and neuroprotective functions [Thiyagarajan et al., 2012]. ANG mutations may lead to loss of either ribonucleolytic activity or nuclear translocation activity [Padhi et al., 2013]. ANG mutations that affect the structure of the catalytic site and increase or decrease the RNase activity, affect neuronal survival [Thiyagarajan et al., 2012]. By application of a fast molecular dynamics based method it seems to be possible to determine the mechanism of functional loss caused by a mutation and the pathogenicity of a mutation [Padhi et al., 2013].

3.1.9. TARDBP (fALS10)

Phenotypically, fALS10 presents as typical ALS phenotype [Chen et al., 2013]. In addition to ALS, FTLD may be part of the presentation [Armstrong and Drapeau, 2013]. fALS10 follows an AD trait of inheritance and is due to mutations in the TARDBP gene encoding TAR DNA-binding protein-43 (TDP-43) [Chen et al., 2013; Iguchi et al., 2013; Xu et al., 2013]. TDP-43 is a highly conserved member of the heterogeneous nuclear ribonuclear protein (hnRNP) family. TARDBP mutations not only cause fALS but also sALS [Daigle et al., 2013]. In a study of 44 sALS and 6 fALS patients from Finnland, no TARDBP mutations were identified [Mentula et al., 2012]. Only non-pathogenic polymorphisms were found [Mentula et al., 2012]. Recently, it has been described that mutant TDP-43 has a higher tendency of β-sheet formation than wild-type TDP-43 [Xu et al., 2013]. Pathologically, accumulation of TDP-43 provokes cytotoxicity and recapitulates pathogenic protein cleavage and insolubility with consecutive proteasomal impairment and dysregulation of the mRNA levels suggesting that increased stability of mutant TDP-43 results in a gain of toxicity through abnormal proteostasis [Watanabe et al., 2013]. In animal studies TARDBP mutations resulted in impairment of neuromuscular junctions [Armstrong and Drapeau, 2013].

3.1.10. FIG4 (fALS11)

fALS11 manifests clinically with prominent, rapidly progressive corticospinal tract signs [Chen et al., 2013]. fALS11 follows an AD trait of inheritance and is due to mutations in the FIG4 gene encoding for phosphoinositide-5-phosphatease a signalling lipid on the cytosolic surface of membranes of the late endosomal compartment [10.14]. It is required for retrograde membrane trafficking from lysosomal and late endosomal compartments to the Golgi apparatus [Iguchi et al., 2013]. In addition to fALS11, FIG4 mutations may cause CMT4J [Chen et al., 2013]. Non-synonymous FIG4 variants have been reported in 2% of the ALS and PLS patients [Chow et al., 2009].

3.1.11. OPTN (fALS12)

fALS12 manifests phenotypically with slowly progressive, limb-onset, predominantly UMN signs [10.14]. In addition to ALS, patients may present with extrapyramidal disease, aphasia, or FTLD [Czell et al., 2013; Kamada et al., 2013; Weishaupt et al., 2013]. Progressive aphasia may be even the presenting symptom in fALS12 [Czell et al., 2013]. fALS12 follows both an AD or AR transmission and is due to mutations in the OPTN gene encoding optineurin, which inhibits nuclear factor κB (NF-κB) [Chen et al., 2013]. In addition to fALS12, OPTN mutations may cause primary open angle glaucoma [Chen et al., 2013]. In a recent study of 100 fALS patients from Germany, a mutation in the OPTN gene was found in only one patient [Weishaupt et al., 2013]. Neuropathological studies in 2 patients with fALS12 carrying the Q398X OPTN mutation have shown that loss-of-function rather than the proteinopathy itself results in the formation of TDF-43 deposits in neuronal and glial cytoplasm and in Golgi apparatus fragmentation [Kamada et al., 2013].

3.1.12. VCP (fALS14)

fALS14 manifests with typical adult-onset ALS with or without FTLD [Chen et al., 2013]. fALS follows an AD transmission and is due to mutations in the VCP gene, encoding valosin-containing protein Refs. [Chen et al., 2013; González-Pérez et al., 2012; Igari et al., 2013]. In addition to fALS14, VCP mutations may manifest as inclusion body myopathy with Paget's disease and FTLD [Chen et al., 2013; González-Pérez et al., 2012; Igari et al., 2013]. Among a cohort of Chinese patients with fALS or sALS, no VCP mutations were found [Zou et al., 2013]. According to an Israeli study, VCP

mutations arise in approximately 1.5% of the fALS cases [González-Pérez et al., 2012].

3.1.13. UBQLN2 (fALS15)

fALS15 manifests phenotypically as UMN signs proceeding to LMN signs [Chen et al., 2013]. fALS15 follows an X-chromosomal transmission (ALSX) and is due to mutations in the UBQLN2 gene encoding ubiquilin-2, involved in the ubiquitin-proteasome system and autophagy [10.14]. UBQLN2 mutations not only cause fALS but also sALS [Daigle et al., 2013]. Recently, is has been shown that single patients carrying UBQL2 mutations may also present with FTLD [5.49]. In a study of 819 cases with sALS, 226 cases with fALS, 53 ALS-FTLD patients, and 63 patients with FTLD, UBQLN2 mutations were found in four fALS patients and in a single sALS patient [Gellera et al., 2013].

3.1.14. SIGMAR1 (fALS16)

fALS16 presents as juvenile-onset typical ALS [Chen et al., 2013]. Single patients may also develop FTLD [Chen et al., 2013]. fALS16 follows an AR transmission and is due to mutations in the sigma receptor-1 (SIGMAR1) gene [Chen et al., 2013]. Recently, mutations in the SIGMAR1 gene have been reported to cause ALS and FTLD [Prause et al., 2013]. The level of the SigR1 protein is reduced in the spinal cord of patients with ALS [Prause et al., 2013]. The sigma receptor-1 protein is abnormally accumulated in the endoplasmatic reticulum of motor neurons [Prause et al., 2013]. There are indications that the sigma receptor-1 is abnormally modified and thus contributes to the pathogenesis of ALS [Prause et al., 2013].

3.1.15. PFN1 (fALS18)

fALS due to mutations in the PFN1 gene, encoding for profilin-1, manifests with classical ALS and FTLD or spinal onset MND without overt cognitive involvement [Daoud et al., 2013; Ingre et al., 2013; Tiloca et al., 2013]. Profilin-1 is a central regulator of actin dynamics [Ingre et al., 2013]. It may be necessary for the fine-tuning of the actin polymerisation by phosphorylation of profilin-1 [Ingre et al., 2013]. PFN1 mutations not only cause fALS but are also involved in sALS [Daigle et al., 2013]. In a study of ALS patients from France and Quebec no mutations in the PFN1 gene have been detected [Daoud et al., 2013]. Among 1168 Italian sALS patients the PFN1 mutations p.E117G or p.G15G were found in a single patient each [Tiloca et al., 2013]. In a study of 412 patients with fALS, 260 patients with sALS, and 16 ALS/FTLD cases from Germany, the Nordic countries, and the US, mutations in the PFN1 gene were found in a single patient from Germany and a single patient from the US [Ingre et al., 2013].

3.1.16. ERBB4 (fALS19)

fALS19 is a late-onset, AD ALS clinically characterised by typical, slowly progressive ALS and a lack of obvious cognitive dysfunction [Takahashi et al., 2013]. fALS19 is due to mutations in the ERBB4 gene, which encodes a receptor tyrosine kinase [Takahashi et al., 2013]. Mutations in ERBB4 lead to reduced autophosphorylation upon neuregulin-1 stimulation [Takahashi et al., 2013].

3.1.17. C9orf72

The C9orf72 phenotype is highly variable even within a family [Cerami et al., 2013]. Affected patients present with pure ALS, ALS + FTD, FTD + ALS, or as pure FTD [Coon et al., 2013]. Commonly, affected patients have a bulbar onset [Iguchi et al., 2013]. Neurons of affected patients show TDP-43 positive aggregates or ubiquitin-positive/TDP-43 negative inclusions [Sabatelli et al., 2013]. There are also patients with semantic deficits with mild ALS features, patients with behavioural variant of FTD, and patients with memory impairment, apathy, and social withdrawal in the absence of ALS features [Cerami et al., 2013]. C9orf72 is the second most common cause of FTLD [Mori et al., 2013]. Among C9orf72 carriers, 40–50% are estimated to develop cognitive impairment [Sabatelli et al., 2013]. Recently, a case with progressive amnestic dementia with restricted TDP-43 pathology has been described [Murray et al., 2013]. In a number of C9orf72 patients onset of the disease is characterised by an MS-like phenotype [Ismail et al., 2013]. Most frequently, these patients present with bulbar symptoms, limb involvement, UMN disease, psychosis (delusions), disinhibition, or apathy [Coon et al., 2013; Takada and Sha, 2012]. Survival is usually short and lasts for 5 y on the average [Coon et al., 2013]. Patients usually die from respiratory failure [Coon et al., 2013]. The pathological profile is characterised by p62-positive but TDP-43 negative cytoplasmic and intranuclear inclusions in cerebellar granular cells and hippocampal pyramidal cells [King et al., 2013].

The intronic GGGGCC repeat expansion between 800 and 4400 repeats (normal: <25 repeats) in the first intron of the C9orf72 gene has been identified as the most common cause of fALS and sALS and familial FTLD but varies between populations from 0 to 18% in Asian countries to 46% in Finnland and France [King et al., 2013; Sabatelli et al., 2013]. In families with ALS/FTD the frequency raises to 50–72% [Sabatelli et al., 2013]. In another study the mutation accounted for 25–34% of the fALS cases [van Blitterswijk et al., 2012a]. In a study of 187 fALS cases and 606 sALS cases the proportion of C9orf72 mutants was 38.5 and 3.5%, respectively [Williams et al., 2013]. Six percent of the fALS cases had developed dementia [Williams et al., 2013]. Among familial FTD cases 12–18% carry the C9orf72 mutation [Sabatelli et al., 2013]. Contrary to Caucasians, the C9orf72 expansion is not the main cause of fALS or sALS in the Korean population [Jang et al., 2013]. Among sALS patients who initially presented with an MS-phenotype, the frequency of C9orf72 hexa-nucleotide repeat expansions is 80% [Ismail et al., 2013]. C9orf72 repeat expansions cause ALS-parkinson-dementia complex in ALS patients from the Kii peninsula but not in the Chamorros from Guam [Dombroski et al., 2013]. C9orf72 expansions are not found in patients with spinocerebellar ataxia [Fogel et al., 2012]. The expanded repeat length is the same in the cerebrum and blood DNA [Pamphlett et al., 2013].

Progression of ALS is more rapid among MS-ALS patients compared to non-MS-ALS patients [Ismail et al., 2013]. MS-associated inflammation is thought to affect penetration and progression of the C9orf72 expansion. The NF-κB pathway is activated in MS-ALS but severely dysfunctional in C9orf72 ALS [Ismail et al., 2013]. Abnormal down-regulation of CXCL10 may explain the predisposition of C9orf72 carriers to develop ALS in the context of MS and NF-κB activation [Ismail et al., 2013]. There is strong phenotypic heterogeneity of FTLD in ALS patients carrying the C9orf72 mutation [Irwin et al., 2013]. Compared to C9orf72-negative patients, C9orf72-positive patients (ALS = 31, FTLD = 33) have an earlier age of onset, an earlier age of death, a more rapid progression, and a shorter survival. Additionally, FTLD in C9orf72-positive has a higher annual rate of decline in letter fluency than in C9orf72-negative patients [Irwin et al., 2013]. Patients carrying the hexa-nucleotide expansion may exhibit the unique features of symmetric frontal and temporal lobe, insular, and posterior cortical atrophy, or cerebellar or thalamic lesions [Yokoyama and Rosen, 2012].

Characteristic intracellular inclusions in C9orf72 associated ALS are built up of poly (Gly–Ala), poly (Gly–Pro), or poly (Gly–Arg) dipeptide-repeat proteins generated by non-ATG-initiated translation from the expanded GGGGCC repeat in three reading frames [Mori et al., 2013]. The G-rich sequences of the GGGGCC expansion have the propensity of forming highly stable quadruplex structures (G-quadruplexes) [Fratta et al., 2012]. The r(GGGGCC)n RNA but not the C-rich r(GGCCCC)n RNA forms extremely stable uni- or

multimolecular parallel G-quadruplex structures [Reddy et al., 2013], which facilitates RNA–RNA interaction and might influence transcript aggregation and foci formation in ALS/FTLD cells [Reddy et al., 2013]. Recently, anti-C9RANT antibodies have been created and shown to specifically bind to neuronal inclusions built-up of insoluble cerebral material [Ash et al., 2013]. Immune-histochemical findings show that the hnRNP A3 (proteins that bind to pre-mRNA) binds to GGGGCC and is involved in the formation of neuronal cytoplasmic and intranuclear inclusions in the hippocampus of ALS patients with C9orf72 repeat expansions [Mori et al., 2013].

3.1.18. DAO

Mutations in the D-amino acid oxidase (DAO) have been shown to cause AD fALS [Iguchi et al., 2013; Paul and de Belleroche, 2012]. DAO regulates D-serine levels and in the presence of a mutation, D-serine levels are elevated. D-serine may be also elevated from induction of the serine racemase, which synthesizes D-serine, by cell stress or inflammatory processes [Paul and de Belleroche, 2012]. Elevated D-serine is regarded to contribute to the disease pathogenesis of ALS.

3.1.19. GRN

Mutations in the GRN gene manifest phenotypically as classical ALS, aphasia, atypical extrapyramidal disorder, or behavioural fronto-temporal dementia [Cannon et al., 2013]. Immune-histochemistry may reveal TDP-43 type A or type B deposition [Cannon et al., 2013].

3.1.20. Dynactin

Dynactin is a protein involved in the retrograde axonal transport clinically manifesting as fALS [Kuźma-Kozakiewicz et al., 2013]. Dynactin is encoded by DCTN1. Recently it has been shown that DCTN1-mRNA is reduced in the motor cortex and spinal cord of sALS patients [Kuźma-Kozakiewicz et al., 2013]. Immunhistochemistry revealed degeneration and loss of neurons and poor expression of dynactin subunits [Kuźma-Kozakiewicz et al., 2013].

3.1.21. SQSTM1

Recently, mutations in the SQSTN1 gene encoding the sequestosome protein 1/p62 have been detected in patients with fALS and sALS [Teyssou et al., 2013]. 1/p62 is a component of inclusions found in ALS patients [Teyssou et al., 2013]. Among 90 fALS patients and 74 sALS patients from France SQSTN1 mutations were detected in one fALS patient and in 3 sALS patients [Teyssou et al., 2013]. SQSTN1 mutations are also associated with M. Paget of the bones [Hirano et al., 2013; Teyssou et al., 2013].

3.1.22. hnRNPA1

Recently, mutations in the PrLD domain of the hnRNPA1 gene were identified to cause fALS and sALS associated with inclusion body myopathy, Paget disease of the bone, and FTD [Calini et al., 2013]. Search for these mutations in a cohort of 113 fALS patients without a mutation failed to detect a hnRNPA1 mutation [Calini et al., 2013].

3.1.23. Erlin2

Juvenile ALS (onset <20 y of age) is clinically distinct from adult ALS. Recently a patient with primary lateral sclerosis (pure UMN affection) has been reported [Al-Saif et al., 2012]. The phenotype was due to a splice-site mutation in the ERLIN2 gene, which encodes a component of the endoplasmatic reticulum lipid rafts [Al-Saif et al., 2012].

3.1.24. UNC13A

Mutations in the UNC13A gene have been identified as modifiers of the prognosis in sALS [van Es et al., 2009]. One year reduction of survival was also found in Italian sALS patients carrying the common variant rs12608932 in the UNC13A gene [Chiò et al., 2013].

3.1.25. ATXN2

Mutations in the ataxin-2 (ATXN2) gene cause spinocerebellar ataxia type 2. They also modify the toxicity of TDP-43 (enhance TDP-43 processing) [Robberecht and Philips, 2013]. Intermediate CAG-repeat expansions (poly-Q) of 27–33 repeats were associated with ALS [Robberecht and Philips, 2013]. Also poly-Q expansions in ATXN1 were associated with ALS [Robberecht and Philips, 2013]. CAG-repeats may be interrupted by 1–3 CAA codons, which seems to influence the disease onset [Robberecht and Philips, 2013]. In a recent study of 405 sALS patients and 13 fALS patients from Italy it has been shown that poly-Q expansion >32 or >28 in the ATXN1 and ATXN2 gene, respectively, increases the risk of ALS [Conforti et al., 2012].

There are a number of other mutated genes responsible for the development of ALS (Table 1] but no new insights were published concerning these items (CHMP2B. NEFH, PRPH, TAF15, EWSR1, spatacsin, and SORT1) during the last year.

3.2. Spinal muscular atrophy (SMA)

In the vast majority of the cases SMA is due to mutations in the survival motor neuron-1 (SMN1) gene (5q-SMA) [He et al., 2013]. Meanwhile, however, it turned out that SMA is genetically heterogeneous and also due to mutations in genes other than the SMN1 (non-5q-SMA).

3.2.1. 5q-SMA

5q spinal muscular atrophy (SMA) is a lethal, AR neurodegenerative disease due to homozygous mutations (deletions, duplications, point mutations) in the SMN1 gene [Lamarca et al., 2013]. In >90% of the cases SMA is due to a homozygous deletion of exons 7 and 8 of the SNM1 gene [He et al., 2013]. Only a minority of patients carries an exclusive deletion of exon 7 [He et al., 2013]. Mutations in the SMN1 gene result in reduced amount of the SMN1 protein, which plays an essential role in the assembly of splicosomal ribonucleoproteins [Branchu et al., 2013; Fallini et al., 2013; Piazzon et al., 2013]. SMN1 is part of a complex essential for splicosomal UsnRNP biogenesis. Reduced SMN1 levels lead to defective signal recognition particles (SRP), ribonucleoprotein particles crucial for co-translational targeting of secretory and membrane proteins to the endoplasmatic reticulum [Piazzon et al., 2013]. In vitro 7S-RNA binds to SMN complexes, which associate with SRPs. An additional role for SMN1 in the axonal transport of RNA-binding proteins and their target mRNAs has been proposed [Fallini et al., 2013]. Recently, a novel mRNA-binding protein, IM91/ZBP1, has been identified and shown that its axonal localisation depends on the amount of SMN1 [Fallini et al., 2013].

Depending on the age at onset and the severity, four types of SMA (SMA 1–4) are differentiated, which each have their distinct genotype depending on the number of SMN2 genes producing residual amounts of fully functional SMN protein or a truncated protein (SMNΔ7). SMA types 1–4 are caused by a homozygous deletion of exons 7 and 8 in the SMN1 gene [Maiti et al., 2012]. Rarely, SMA types 2 and 3 are due to isolated deletion of exon 8 of the SMN1 gene [Maiti et al., 2012]. Recently, it has been found that SMA is not confined to motor neurons but may also affect other organs, such as the brain, myocardium, or pancreas, clinically manifesting as epilepsy, heart failure, cardiac malformations, or

diabetes [Lamarca et al., 2013]. Additionally, optic atrophy has been reported as a manifestation of SMA [Maiti et al., 2012]. Rarely, ophthalmoparesis may be associated with SMA [Maiti et al., 2012].

SMA-phenotype and disease severity of SMA are modulated by several genes nearby SMN1 in the 15q13 region, such as SMN2, NAIF, GTF2H2, and H4F5 [He et al., 2013]. The most well-known of these modifiers is SMN2, which provides a small amount of stable SMN1 protein [Branchu et al., 2013]. Severity of the phenotype may be also enhanced by an additional deletion in the neural apoptosis inhibitory protein (NAIP) gene [Maiti et al., 2012]. In humans SMN2 is nearly identical to SMN1 and SMN1 deletions are compensated by SMN2. All patients retain one or more copies of the SMN2 gene, which modulate disease severity [Branchu et al., 2013]. SMA develops only if SMN2 is unable to compensate for the SMN1 absence, which is the case if dysfunctional SMN2 due to skipping of exon 7 leads to the production of a truncated SMN2 [Seo et al., 2013]. In a mouse model expression of SMN2 could be enhanced by inhibition of the MEK/ERK/Elk1 pathway, which promotes the activation of the AKT/CREB pathway [Branchu et al., 2013]. There is an inverse relation between disease severity and the copy number of SMN2 or NAIP [He et al., 2013]. Severe type I patients may carry a deletion of exons 7 and 8, and deletions of NAIP and GFT2H2 [He et al., 2013].

3.2.2. Non-5q-SMA

3.2.2.1. Motor adaptor BICD2 SMA. Mutations in the motor adaptor BICD2 gene result in an AD SMA-phenotype characterised by proximal onset in early childhood with predominant involvement of the lower extremities, and very slow progression [Peeters et al., 2013]. BICD2 mutations cause increased dynein-binding leading to accumulation of BICD2 in the microtubule-organising complex and Golgi-fragmentation [Peeters et al., 2013]. BICD2 mutations additionally result in reduced colocalisation with RAB6A, a regulator of vesicle trafficking between the Golgi apparatus and the endoplasmatic reticulum [Peeters et al., 2013].

3.3. Bulbospinal muscular atrophy (BSMA)

BSMA is an X-linked MND with onset in adulthood caused by a CAG-triplet repeat expansion in the androgen receptor (AR) gene [Minamiyama et al., 2012]. The mechanism underlying gain-of toxic function is not fully understood but there are indications that nuclear and cytoplasmic AR aggregates play an important role [Kumar, 2012]. The interaction of AR with several coactivators is modulated by the AR conformational state and aberrant poly-Q tract [Kumar, 2012]. A main target of the AR seems to be FUS, which partially would explain the phenotype [Fratta et al., 2013]. However, in a mouse model of BSMA there were no indications of FUS dysregulation [Fratta et al., 2013]. Recently, it has been shown that the mutated AR upregulates the CGRP1 gene encoding the calcitonin gene-related peptide-α [Minamiyama et al., 2012]. Overexpression of CGRP1 is cytotoxic. Suppression of CGRP1 suppresses neurodegeneration at least in mice [Minamiyama et al., 2012]. Suppression of CGRP1 can be achieved by application of naratriptan, a serotonin receptor agonist [Minamiyama et al., 2012].

3.4. Unclassified MNDs

3.4.1. Sandhoff disease

A rare form of MND is Sandhoff disease with an MND phenotype due to mutations in the HEXB gene encoding the β-subunit of the β-hexosaminidase (GM2-gangliosidosis) [Yamada et al., 2013]. In a family carrying the H235Y mutation in the β-sheet of the (β/α) s-barrel domain of the β-subunit, the mutation abolished the α–β and β–β dimer formation [Yamada et al., 2013]. Novel mutations in the β-subunit of the β-hexosaminidase gene (c-512-13C > A, c.1613 + 15_1613 + 18dup) have been also reported in juvenile cases of the disease [Pierson et al., 2013]. Mutations in the HEXA may lead to SMA accompanied by cerebellar and extrapyramidal symptoms during the course [Jamrozik et al., 2013]. These patients have normal intelligence but cerebellar atrophy and glucose hypermetabolism in the cerebellum and the temporal and occipital lobes bilaterally on PET scans [Jamrozik et al., 2013].

3.4.2. Triple-A-syndrome

Mutations in the ALADIN gene, encoding for a nuclear pore complex component, cause triple-A-syndrome [Ikeda et al., 2013]. Triple-A-syndrome is an AD disease, mimicking MND, characterised by esophageal achalasia, alacrimia, adrenal insufficiency, progressive bulb spinal muscular atrophy with involvement of the UMN and LMN [Ikeda et al., 2013]. Triple-A-syndrome mimics MND and follows an AR trait of onheritance. Mutations in the ALADIN gene, encoding for a nuclear pore complex component, are associated with triple-A-syndrome [99].

3.4.3. Brown–Vialetto–Van Lare syndrome

Brown–Vialetto–Van Lare syndrome, also known as Fazio–Londe syndrome, mimics bulbar ALS since it presents with bulbar palsy, respiratory compromise, and sensorineural hearing loss [Bosch et al., 2012]. Recently, it has been shown that the syndrome is most likely due to mutations in the SLC52A1 gene encoding the human riboflavin transporter hRFT1 [Bosch et al., 2012]. Substitution of riboflavin seems to have a beneficial effect with significant prolongation of life expectancy [Bosch et al., 2012].

4. Discussion

There is increasing evidence that the classification of ALS into sALS and fALS cases is artificial as mutated genes are increasingly recognised also in sALS cases. Both, fALS and sALS, present with similar clinical manifestations and pathology (e.g. ubiquitinated TDP-43 positive inclusions) and heredibility is increasingly addressed also in sALS cases [Sabatelli et al., 2013]. A number of mutated genes responsible for fALS can be also found in sALS cases. In a study of 480 apparently sALS cases a mutation in one of the major fALS genes was found in 11% of the sALS patients [Lattante et al., 2012]. In a study of adult sALS patients mutations were found in SOD1 ($n = 2$), ANG ($n = 1$), FUS/TSL ($n = 1$), TARDBP ($n = 1$), and CHMP2B ($n = 1$) [van Blitterswijk et al., 2012b]. Reasons for missing the genetic background in sALS may be inaccuracy in the definition of fALS, insufficient family history, misdiagnosis of ALS in other family members, early death prior to developing ALS, small family size, pleotropy of phenotype as in C9orf72, FUS, TARDBP, OPTN, FIG4 and ANG mutations [Andersen and Al-Chalabi, 2011], de novo mutations, double mutations [Lattante et al., 2012], or low penetrance of a mutation [Sabatelli et al., 2013]. According to the low-penetrance susceptibility model, a polygenic threshold model, sALS results from summation of various low-frequency, weakly deleterious mutations in a number of different genes, of which each increases the relative risk [Simpson and Al-Chalabi, 2006].

Among the various genes found to have been responsible for fALS only a limited number is responsible for a considerable proportion of fALS cases [Sabatelli et al., 2013]. These genes include C9orf72, SOD1, TARDBP, and FUS [Sabatelli et al., 2013]. All other genes are usually found only in a limited number of patients. This is why Caucasian fALS cases with an onset >60 y should be initially screened for these four most frequently mutated genes. In a study of 476 ALS patients from Piemont, 10.7% carried a mutation in one of the known fALS genes [Chiò et al., 2012]. The most frequent mutation was the C9orf72 expansion ($n = 34$), followed by SOD1

($n = 10$), TARDBP ($n = 7$), FUS ($n = 1$), and OPTN ($n = 1$) [Chiò et al., 2012]. Comorbid FTLD or young age were strong indicators of a possible genetic origin of ALS [Chiò et al., 2012]. In juvenile fALS cases (onset <20 y) genes most frequently mutated include ALS2, SETX, spatacsin, and Sigmar1. Concerning the phenotypic variability between the different genes, there is a significantly higher frequency of cognitive impairment in patients carrying the C9orf72 mutation than in non-C9orf72 patients [Byrne et al., 2012]. Cognitive impairment is particularly rare in SOD1 patients [Chiò et al., 2012]. In C9orf72 patients, bulbar onset seems more frequent and survival shorter than in other ALS patients [Ratti et al., 2012]. As only in 50–60% of the fALS cases mutations in currently known genes can be found, detection of other new genes in the future can be expected. This will also increase the proportion of sALS cases with a genetic aetiology.

5. Conclusions

Progress has been made over the last year in the clarification and understanding of the aetiology and pathogenesis of MNDs. However, further effort is needed to find answers to the many remaining open questions. More insights are required particularly for developing effective treatments of these devastating diseases. Future studies will show if the novelties provided in this review truly have changed our understanding and provided the basis for further steps.

Conflict of interest

There is no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interest of the authors, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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