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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