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Review

Motor neuron disease and frontotemporal dementia: sometimes related, sometimes not

John Hardy [a,*], Ekaterina Rogaeva [b]

[a] Reta Lilla Weston Research Laboratories and Department of Molecular Neuroscience, UCL Institute of Neurology, London WC1N 3BG, UK
[b] Tanz Centre for Research in Neurodegenerative Diseases and Department of Medicine, Division of Neurology, University of Toronto, 6 Queen's Park Crescent West, Toronto, ON M5S 3H2, Canada

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ABSTRACT

Over the last 5 years, several new genes have been described for both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). While it has long been clear that there are many kindreds in which the two diseases co-occur, there are also many in which the diseases segregate alone. In this brief review, we suggest that keeping the loci which lead to both diseases separate from those which lead to just one gives a clearer conclusion about disease mechanisms than lumping them together. The hypothesis that this separation leads to is that loci which cause both ALS and FTD affect the autophagic machinery leading to damaged protein aggregation and those which lead to just ALS are mainly involved in RNA/DNA metabolism. Two of the genes causing FTD alone (CHMP2B and GRN) are associated with damaged autophagy/lysosomal pathway. However, the third FTD gene (MAPT) maps to a different pathway, which perhaps is not surprising, since it is associated with a different (not p62-related) brain pathology characterized by abnormal tau filaments. We conclude that the current state of knowledge points to common mechanisms responsible for susceptibilities specific to neuronal classes. This includes the disruption of RNA metabolism in motor neurons and protein clearance, which is common between cortical and motor neurons.

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Introduction

Recently, frontotemporal dementia (FTD; MIM: 600274) and amyotrophic lateral sclerosis (ALS; MIM: 612069) have been considered to constitute a neurodegenerative syndrome, with patients presenting

* Corresponding author.
E-mail address: j.hardy@ucl.ac.uk (J. Hardy).

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along a clinical spectrum. The fact that this can occur has been documented for ~80 years (Van Bogaert, 1925). Patients with pure FTD exhibit primary dementia often characterized by early behavioral problems and speech pathology; while patients with pure ALS are characterized by the degeneration of motor neurons affecting voluntary movements. Both syndromes may happen within the same family or even the same individual.

The first identified mendelian cause of ALS is mutations in the SOD1 gene (Rosen et al., 1993), and the first identified mendelian cause of FTD is mutations in the MAPT gene (Hutton et al., 1998). In both of these conditions, while the phenotypes of SOD1 or MAPT mutation carriers have been variable, they have always been clearly within the spectra of ALS and FTD, respectively. However, the identification of mutations in TARDBP (Sreedharan et al., 2008) and FUS (Kwiatkowski et al., 2009) for ALS and mutations in GRN (Baker et al., 2006; Cruts et al., 2006) and CHMP2B (Skibinski et al., 2005) for FTD, followed by the apparent detection of mutations in these genes in patients with either of these disorders (Broustal et al., 2010; Cox et al., 2010; Huey et al., 2012; Parkinson et al., 2006; Van Langenhove et al., 2010) has added to the idea of an ALS–FTD continuum. In addition, the recent identification of mutations in VCP (Johnson et al., 2010; Watts et al., 2004), SQSTM1 (Fecto et al., 2011; Le Ber et al., in press; Rubino et al., 2012), OPTN (Kamada et al., 2013; Maruyama et al., 2010), UBQLN2 (Deng et al., 2011; Vengoechea et al., 2013) and especially the $(G_4C_2)_{n>30}$ repeat expansion in C9orf72 (DeJesus-Hernandez et al., 2011; Renton et al., 2011) in both disorders has also fostered the notion of a continuum.

Setting aside the SOD1 and MAPT mutations, which clearly give rise to distinct disorders based on clinical and neuropathological features (ALS and FTD respectively), we need to systematically examine the evidence for the other genes mentioned above as causes of both diseases before we try and map them onto common biochemical pathways.

FUS

According to the Mutation Database, multiple mutations in the FUS gene (missense substitutions or in-frame small deletions/insertions) have been shown to segregate with ALS6 (MIM: 608030) (Cruts et al., 2012). The disease associated with FUS may present as an incompletely penetrant, recessive or sporadic disorder, however most of the families demonstrate an autosomal dominant mode of inheritance. The frequency of FUS mutations in familial ALS is ~5%. Half of the 23 pathogenic mutations affect the last FUS exon #15 containing a nuclear localization signal. Another mutation hot-spot is exon #6 encoding for a part of the Gly-rich low-complexity (prion-like) domain. Of note, there is substantial genetic variability in the FUS gene in normal controls (Huey et al., 2012), and some of the FUS mutations reported in patients have poor support for their pathogenic nature, such as lack of segregation with disease and/or autopsy results. For instance, FUS variants with a questionable pathogenic nature, such as Pro106Leu, Gln179His (Huey et al., 2012) and Met254Val (Van Langenhove et al., 2010), were reported in a few FTD patients. Hence, there is no strong evidence that FUS is genetically involved in FTD; however the brain pathology of ~5% of FTD patients is associated with FUS-proteinopathy (Sieben et al., 2012).

The FUS protein is a component of the complex regulating sensors of DNA damage. Apart from DNA repair, FUS is also important for mRNA/microRNA metabolism (e.g. regulation of transcription and RNA splicing) (Vance et al., 2009). Normally FUS is mainly localized to the nucleus, while the mutant FUS protein is retained in the cytoplasm, thus interfering with nuclear function. Brain pathology of FUS-related ALS (with or without FUS mutations) is associated with motor neuron loss in the spinal cord, brainstem and motor cortex accompanied by nuclear and cytoplasmic aggregation of FUS in neurons and glial cells, as well as with diffuse ubiquitin positivity in nuclei, suggesting the presence of misfolded protein (Vance et al., 2009).

TARDBP

Multiple heterozygous TARDBP mutations have been described as a cause of ALS10 (MIM: 612069), many of which have been shown to segregate with disease in an autosomal dominant mode of inheritance and explain ~3% of patients with familial ALS (Cruts et al., 2012). Almost all clearly pathogenic mutations (33 of 34) are missense substitutions (apart from a frame-shift mutation; Tyr374X), and affect codons 263 to 393 in the last TARDBP exon #6 encoding a Gly-rich low-complexity (prion-like) domain, similar to FUS. Only three mutations were reported in FTD (Lys263Glu; Asn267Ser) or FTD/ALS (Gly295Ser), without evidence of segregation with the FTD phenotype. One of the most common TARDBP mutations in ALS (Ala382Thr) was found in a homozygous state in two siblings from a consanguineous Italian family, one of which was diagnosed with Parkinson's disease (at age 61) followed by ALS/FTD six years later; while his 67 years old brother did not show any neurological signs (Mosca et al., 2012). This observation does not suggest a more severe phenotype in homozygous versus heterozygous TARDBP carriers.

There are many functional similarities between the FUS and TARDBP gene that encodes the 43-kD TAR DNA-binding protein (TDP43), which is normally localized to the nucleus and involved in regulation of gene expression and splicing, while in disease it is relocated to cytoplasm leading to a loss of nuclear function (Neumann et al., 2006). A pathologic form of TDP43 is hyperphosphorylated, ubiquitinated, and cleaved, and constitutes a major component of the nuclear and cytoplasmic inclusions observed in neuronal and glial cells of the majority of ALS cases (with or without TARDBP mutations). Furthermore, brain pathology with TDP43-inclusions is a common link between several sporadic and inherited neurodegenerative conditions including FTD, as discussed below. Intriguingly, the results from transgenic TDP43 mice suggest that the detected signs of neurodegeneration are related to altered DNA/RNA-binding protein function rather than to toxic aggregation, since cytoplasmic TDP43 aggregates were absent in mutant mice (Wegorzewska et al., 2009).

C9orf72 (DENNL72)

The heterozygous hexanucleotide $(G_4C_2)_{n>30}$ repeat expansion in the non-coding region of the C9orf72 gene clearly causes both FTD and ALS (MIM: 105550); and for both diseases genetic linkage and association has been reported (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Currently, the repeat expansion accounts for 24–37% of familial and 6–7% of sporadic cases in whites (Majounie et al., 2012; Rademakers, 2012).

Hypotheses about the disease mechanism associated with the repeat expansion include toxic gain of function based on either the sequestering of RNA binding proteins by RNA foci consisting of pre-mRNA with the expansion (DeJesus-Hernandez et al., 2011); or the non-ATG-initiated translation from the expansion (in different reading frames) leading to the aggregation of dipeptide-repeat proteins in neurons (Ash et al., 2013; Mori et al., 2013). Another possibility is a loss of function mechanism, since the expansion is associated with hypermethylation of the CpG-island 5′ of the repeat (Xi et al., 2013) and ~50% reduction of C9orf72 mRNA in carriers (DeJesus-Hernandez et al., 2011). Of note, methylation changes were not detected in either normal or intermediate alleles (up to 43 repeats), raising the question of whether the cutoff of 30 repeats for pathologic alleles is adequate. Importantly, in several other disorders (e.g. Friedreich ataxia) repeat expansions lead to DNA hypermethylation and a down-regulation of gene expression (Xi et al., 2013). However, it seems unlikely that the main mechanism of the C9orf72 mutation is a loss of function because other segregating loss of function variants have not been found (e.g. stop codon mutations). Also, the only report of a homozygous repeat expansion in a patient with early-onset pure FTD rather supports a gain of toxic function mechanism, since the patient's clinical/pathological

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