Neuroscience and Biobehavioral Reviews 74 (2017) 126–138

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Mouse models of frontotemporal dementia: A comparison of phenotypes with clinical symptomatology

Rebekah M. Ahmed[a,b,c], Muireann Irish[a,b,d,j], Janet van Eersel[e], Arne Ittner[e], Yazi D. Ke[e], Alexander Volkerling[e], Julia van der Hoven[e], Kimi Tanaka[e], Tim Karl[a], Michael Kassiou[f], Jillian J. Kril[g], Olivier Piguet[a,b,h,j], Jürgen Götz[i], Matthew C. Kiernan[c], Glenda M. Halliday[a,h,j], John R. Hodges[a,b,h,j,*], Lars M. Ittner[a,e,*]

[a] Neuroscience Research Australia, Sydney, Australia
[b] ARC Centre of Excellence in Cognition and its Disorders, the University of New South Wales, Sydney, Australia
[c] Sydney Medical School, Brain & Mind Centre, University of Sydney, Australia
[d] School of Psychology, the University of New South Wales, Sydney, Australia
[e] Dementia Research Unit, Department of Anatomy, School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia
[f] Faculty of Health Sciences, The University of Sydney, Australia
[g] Discipline of Pathology, Sydney Medical School, The University of Sydney, Australia
[h] School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia
[i] Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia
[j] Brain and Mind Centre, University of Sydney, Australia

ARTICLE INFO

Article history:
Received 13 September 2016
Received in revised form 4 January 2017
Accepted 6 January 2017
Available online 11 January 2017

Keywords:
Frontotemporal dementia
Transgenic
Mouse
Amyotrophic lateral sclerosis
Behavioural neurology

ABSTRACT

Frontotemporal dementia (FTD) is the second most common cause of young onset dementia. It is increasingly recognized that there is a clinical continuum between FTD and amyotrophic lateral sclerosis (ALS). At a clinical, pathological and genetic level there is much heterogeneity in FTD, meaning that our understanding of this condition, pathophysiology and development of treatments has been limited. A number of mouse models focusing predominantly on recapitulating neuropathological and molecular changes of disease have been developed, with most transgenic lines expressing a single specific protein or genetic mutation. Together with the species-typical presentation of functional deficits, this makes the direct translation of results from these models to humans difficult. However, understanding the phenotypical presentations in mice and how they relate to clinical symptomology in humans is essential for advancing translation. Here we review current mouse models in FTD and compare their phenotype to the clinical presentation in patients.

Contents

* Corresponding authors at: Neuroscience Research Australia, Barker St. Randwick, NSW, 2031, Australia (Lars Ittner) and Brain and Mind Centre, University of Sydney, 94 Mallett st. Camperdown 2006 (John R. Hodges).
E-mail addresses: john.hodges@sydney.edu.au (J.R. Hodges), l.ittner@unsw.edu.au (L.M. Ittner).

http://dx.doi.org/10.1016/j.neubiorev.2017.01.004
0149-7634/

1. Introduction

The term frontotemporal dementia (FTD) refers to a group of neurodegenerative disorders characterized by atrophy of the frontal and anterior temporal lobes of the brain. Prevalence studies suggest that FTD is the second most common cause of young onset dementia (Ratnavalli et al., 2002; Rosso et al., 2003). Two main clinical syndromes of FTD exist, based on the predominant clinical features at presentation: behavioural variant FTD (bvFTD), where there is deterioration in social function and personality; and primary progressive aphasia (PPA), with an insidious decline in language skills. PPA is further subdivided based on the nature of language breakdown into semantic variant primary progressive aphasia (sv-PPA), and non-fluent or agrammatic aphasia (progressive non-fluent aphasia: PNFA) (Gorno-Tempini et al., 2011; Hodges and Patterson, 2007). FTD overlaps with ALS at a clinical, genetic and pathological level (Mitsuyama and Inoue, 2009), a position confirmed with the discovery of the *C9ORF72* repeat expansion in FTD, FTD-ALS and ALS cases (Hodges, 2012).

Each of the FTD syndromes presents with distinct clinical symptoms, neuroimaging, and pathological profiles (Table 1). Considerable overlap and heterogeneity exist within and between the syndromes, with limited correlations between clinical phenotype, underlying pathology and genotype. Given this complexity, the development of animal models of FTD has proven difficult. Currently available mouse models focus on the genetic causes and pathological changes and these only imperfectly correlate with clinical phenotypes. Here, we review current transgenic mouse models and compare their phenotypes to clinical features and functional deficits in FTD, which may guide the development of disease-modifying therapies.

2. Pathology of FTD

Both sporadic and autosomal dominant FTD are associated with a range of underlying pathologies, classified according to the protein predominantly accumulating in patients' brains. These proteins include the microtubule-associated protein tau, with different tau isoforms being affected in FTD subtypes such as 4-repeat tau (progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) or globular glial tauopathy (GGT)) that is characterized neuropathologically by widespread globular oligodendroglial and astrocytic tau inclusions (Ahmed et al., 2013), 3-repeat tau (Pick's disease), and mixed 3- and 4-repeat tau forms; TAR-DNA binding protein (TDP)-43 (type A to D; for details see (Mackenzie et al., 2011)); and fused in sarcoma (FUS). In bvFTD, any of these pathological variants can be found, with tau or TDP-43 positive cases found at similar frequencies (Josephs et al., 2011; Seelaar et al., 2011). In sv-PPA the predominant pathology is TDP type C (Josephs et al., 2011; Rohrer et al., 2010). The pathology of the other language variants is more variable and includes tauopathies, and TDP-43 proteinopathies. The co-occurrence of FTD and ALS is strongly suggestive of an underlying TDP-43 pathology (typically type B) (Seelaar et al., 2011). Recent research has suggested that FTD and ALS may potentially result from a contiguous (almost 'prion-like') spread (Braak et al., 2013; Ludolph and Brettschneider, 2015; Tan et al., 2015). This occurs in a recognised centrifugal pattern with 4 stages of spread in ALS beginning in the motor neocortex, progressing to the spinal cord and brainstem, with involvement of fronto-parietal regions and finally the temporal lobes (Brettschneider et al., 2013). Such a pattern of spread may explain the development of cognitive symptoms in ALS and the spectrum of ALS and FTD. In behavioural variant FTD (bvFTD) pathological spread has been suggested to develop with a fronto-occipital gradient involving initially the frontal regions, and then pre-motor, primary motor, parietal and occipital cortex (Brettschneider et al., 2014).

3. Genetic causes of FTD

About 25–33% of FTD patients have a family history with an autosomal dominant pattern of inheritance (Rohrer et al., 2009; Rohrer and Warren, 2011; Rohrer et al., 2015a; Rohrer et al., 2015b), most commonly associated with bvFTD (Seelaar et al., 2008). The three most common genes involved in FTD are *C9ORF72*, microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*). Mutations in other, much less frequent, gene loci include *VCP*, *CHMP2B*, *FUS*, *TARBP*, *DCTN1* and *SQSTM1*. The frequency of each mutation varies according to the geographical location. In a USA-based cohort (DeJesus-Hernandez et al., 2011) *C9ORF72* was the most common mutation, whereas in a Dutch cohort (Simon-Sanchez et al., 2012) *MAPT* mutations were more common, and in a UK-based cohort *C9ORF72* expansions and *MAPT* mutations occurred with equal frequency (Mahoney et al., 2012). Clinical phenotypes vary across the different genetic syndromes, but certain phenotypes are more commonly associated with specific mutations. For *GRN* mutations, the most common phenotypes are bvFTD, followed by PNFA and corticobasal syndrome (Chen-Plotkin et al., 2011; Yu et al., 2010). *MAPT* mutations are also most frequently associated with bvFTD, but language presentations