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REVIEW

Expanding the genetics of amyotrophic lateral sclerosis and frontotemporal dementia

Jennifer C Schymick*[1,2] and Bryan J Traynor[2]

Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized clinically by rapidly progressive paralysis leading ultimately to death from respiratory failure. It is now recognized that ALS and frontotemporal lobar degeneration (FTLD) form a clinical spectrum of disease with overlapping clinical, pathological and genetic features. This past year, the genetic causes of ALS have expanded to include mutations in the genes *OPTN*, *VCP*, and *UBQLN2*, and the hexanucleotide repeat expansion in *C9ORF72*. The *C9ORF72* repeat expansion solidifies the notion that ALS and FTLD are phenotypic variations of a disease spectrum with a common molecular etiology. Furthermore, the *C9ORF72* expansion is the genetic cause of a substantial portion of apparently sporadic ALS and FTLD cases, showing that genetics plays a clear role in sporadic disease. Here we describe the progress made in the genetics of ALS and FTLD, including a detailed look at how new insights brought about by *C9ORF72* have both broadened and unified current concepts in neurodegeneration.

Defining the overlap between ALS and FTLD: a necessary first step in unraveling the genetics of both conditions

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, uniformly fatal, neurodegenerative disease. The annual incidence of ALS is reported to be 1.5 to 2.7 per 100,000 in Western countries [1,2]. There is currently no cure for ALS, and approximately 6,500 individuals die from the disease each year in the United States, making it the most common adult-onset form of motor neuron disease, and the third most common form of neurodegeneration [3]. Median age of symptom onset is between 65 and 67 years, meaning that ALS is often considered to be a disease associated with aging [4].

An important historical fact is that Jean Martin Charcot first defined ALS as a pure motor neuron disease [5]. Since then, the traditional view has been that cognition remains intact in the majority of ALS patients except for a small proportion who developed florid dementia (approximately 5% of cases). This view has only relatively recently been challenged and the current consensus is that ALS and frontotemporal lobar degeneration (FTLD) form part of a continuum of neurological disease: patients with familial and sporadic ALS exhibit signs of frontal lobe degeneration, including language dysfunction, changes in personality and executive function with relative sparing of memory [6-9]. Similarly, FTLD is complicated by motor neuron dysfunction in a significant proportion of patients. These observations directly led to diagnostic criteria categorizing cognitive and behavioral dysfunction in ALS [10].

The concept that ALS and FTLD represent a continuum of disease was further supported by neuropathological evidence concerning the abnormal protein aggregates observed in degenerating neurons. Initially, immunoreactive, ubiquitin-positive neuronal inclusions were identified in ALS and FTLD and provided a first clue of a shared pathogenic mechanism between these conditions. Then, in 2006, the TAR DNA-binding protein 43 kDa (TDP-43) was discovered to be the main component of the ubiquinated inclusions [11]. In 2009, aggregations of the fused in sarcoma protein (FUS) were demonstrated in a subset of ALS and FTLD patients with TDP-43-negative neuronal inclusions (representing approximately 5% of cases) [12]. Following these discoveries, it was proposed that ALS and FTLD form a clinicopathological spectrum of TDP-43 and FUS proteinopathies [13], though it is also noteworthy that approximately 40% of FTLD cases are tauopathies and there is currently no known relationship between such cases and ALS.

Why is this overlap between ALS and FTLD important to our discussion about genetics? The realization that ALS and FTLD are essentially two sides to the same neurodegenerative coin allowed the identification of several families in which the conditions co-existed. The

*Correspondence: schymicj@hs.uci.edu
[1]University of California Irvine School of Medicine, Irvine, CA 92697, USA
Full list of author information is available at the end of the article

large number of affected individuals available for study in these ALS/FTLD families increased the linkage value of these families, and consequently their power to find new genes.

State of play of ALS and FTLD genetics before the *C9ORF72* discovery

Population-based epidemiological studies show that approximately 5% of ALS is familial in nature, with a predominantly autosomal dominant pattern of inheritance [1]. The remaining 95% of cases do not have a family history of ALS, and appear to occur sporadically throughout the community. The clinical characteristics of familial and sporadic ALS are nearly indistinguishable, and it has long been hoped that understanding familial ALS would shed light on the fundamental processes underlying the pathogenesis of the more common sporadic form of the disease. At least that was the theory…

Substantial progress had been made over the past 20 years in our understanding of the genetic factors contributing to familial ALS. These include the identification of mutations in the *SOD1* gene in 1993, which account for approximately 12% of familial ALS cases in population-based studies [14,15]. There was then a long hiatus until mutations in the *TARDBP* gene, which encodes the TDP-43 protein, were found in 2008 [16]. This was followed quickly by the discovery of mutations in the *FUS* gene as the cause of chromosome 16-linked ALS [17,18]. Each of these genes accounted for approximately 4% of familial ALS cases.

More recently, the pace of genetic discovery has accelerated due to advances in genomic sequencing technologies. This led to the discovery of additional familial ALS genes, including *OPTN*, *VCP*, and *UBQLN2* [19-21]. The discovery of *VCP* was particularly important in that regard, as it was previously known to cause FTLD, further strengthening the genetic link between these two neurodegenerative disorders. Although the discovery of each of these genes represented a quantum leap forward in our understanding of the pathogenic pathways underlying motor neuron degeneration, these mutations together only accounted for a quarter of familial ALS cases. Clearly, additional genes remained to be found.

But how well did these findings in familial ALS translate to the more common sporadic form of the disease? Truth be told, the genetics of sporadic ALS were proving much more difficult to unravel [22,23]. Mutations in the known familial ALS genes - *SOD1*, *FUS*, *TDP-43*, and *VCP* - occur only rarely in sporadic cases [15,24-26]. As a consequence, the prevailing hypothesis was that environmental factors were more relevant in the sporadic form of the disease. Nevertheless, advances in genomic technology made it far more attractive to chase the genetics of sporadic ALS, rather than focusing on proving environmental hypotheses [27]. Research in other neurological diseases, most notably Parkinson's disease, confirmed that genetics could be a key driving force in neurodegeneration [28]. This view was reinforced by the occasional finding of *de novo* mutations of known familial ALS genes in young patients with sporadic ALS [29-31].

Identification of chromosome 9 as an important player in ALS and FTLD

The long arm of chromosome 9 was initially linked to ALS and FTLD in a 2000 *Journal of the American Medical Association* paper [32]. This initial locus was later refined to involve the short arm of chromosome 9 in 2006 with the publication of two papers reporting linkage to the region in large Dutch and Scandinavian ALS-FTLD families [33,34]. The initial genetic area defined by these studies was further shortened to a 7.1 MB region by the publication of several additional linkage studies [35-38].

From an early stage it was apparent that chromosome 9p21 was an important locus in ALS and FTLD, as it appeared to underlie a large proportion of familial ALS cases. Interest was further raised when ALS and FTLD genome-wide association studies consistently found an association signal within the chromosome 9 locus [39-42]. These studies narrowed the area of interest to a relatively small 232 kb region of the genome located at chromosome 9p21, containing only three genes (*MOBLK2B*, *IFNK*, and *C9ORF72*). Bizarrely, the underlying mutation was proving difficult to find despite the small size of the region of interest. As time went by, the whole locus looked increasingly intractable and a 'Holy Grail' aura developed around it.

Our own genome-wide association study of ALS in Finland identified a 42-SNP founder haplotype that segregated within ALS/FTLD families. Informed by that observation, we believed from an early stage that the chromosome 9p21 locus was due to a founder mutation [39,43], though this notion was rebuffed by other groups studying the same region [40].

C9ORF72 revealed

Ultimately, a massive hexanucleotide repeat expansion in the *C9ORF72* gene was found to be the mutation underlying chromosome 9p21. Back-to-back publications appeared in the October 2011 edition of *Neuron* revealing the causative mutation to be a massively expanded GGGGCC hexanucleotide repeat expansion [44,45]. This expansion accounted for an exceptionally large proportion of both familial ALS and FTLD, as well as a large proportion of sporadic ALS and FTLD. These publications represented the culmination of three years of intense national and international collaboration [46]. The finding was subsequently replicated by independent groups in different populations [47,48].

Only a short period of time has passed since the discovery of the *C9ORF72* repeat expansion, but already certain aspects are becoming clear. The pathogenic expansion on chromosome 9p21 is by far the most frequent cause of ALS and FTLD identified to date, being at least twice as common as *SOD1* mutations in ALS, and as *PGRN* mutations in FTLD. The discovery of the hexanucleotide repeat expansion increased the proportion of familial ALS that was explained from one-quarter to nearly two-thirds. It also showed that genetics plays a major role in apparently sporadic ALS and FTLD, thereby unifying the two major forms of the disease: in a large cohort of white Europeans, Americans, and Australians the *C9ORF72* repeat was identified in approximately 6% of both sporadic ALS and FTLD cases [49]. Patients with pure ALS, pure FTLD, or ALS-FTLD have 700 to 1,600 repeats that may be up to 10 kb in length, whereas people without these diseases have fewer than 24 repeats [44,45].

But what does *C9ORF72* do?

The key question among researchers at the moment is 'what is the normal function of *C9ORF72*' and 'by what cellular mechanism does the pathogenic repeat expansion lead to neurodegeneration?' *C9ORF72* encodes a highly conserved, 481 (full-length) amino acid protein. The protein has no discernable domains, and consequently, little is known about its function. There are three reported splice variants with the pathogenic repeat expansion variably lying within the promoter or first intron of the different transcripts [44,45].

Different mechanisms of disease can be postulated for any of the repeat expansion disorders, including loss of function, gain of function due to abnormal RNA toxicity, or gain of function due to abnormal protein toxicity [50]. At the present time, it is unclear which of these mechanisms is operating in *C9ORF72*-ALS, and there are conflicting data for each: the location of the repeat directly within the promoter of the long *C9ORF72* transcript suggests the possibility that the expansion alters *C9ORF72* expression, at least of this isoform. Altered *C9ORF72* transcription is supported by both original *Neuron* papers, which identified reduced expression of the longer mRNA isoforms in brain [44,45]. On the other hand, most of the autopsy-confirmed mutation carrier patients had TDP-43 inclusions in brain or spinal cord, indicating that abnormal protein accumulation is important, regardless of the initiating cellular mechanism [51,52]. Furthermore, the RNA inclusions reported in the original DeJesus-Hernandez *et al*. paper [44] suggest that toxic RNA species generated from the expansion may be important. So far these initial findings have proven difficult to replicate, perhaps because of the technical difficulties inherent in *in situ* hybridization [53,54].

Clinical characteristics of *C9ORF72*-associated disease

Clinically, *C9ORF72* expansion cases with motor neuron dysfunction show features of classical ALS with a relatively rapidly progression. Disease duration was six months shorter in ALS cases with *C9ORF72* expansions compared with the non-*C9ORF72* ALS cases [51]. Bulbar-onset disease was also more common in patients with the *C9ORF72* mutation compared to non-*C9ORF72* ALS cases [55]. *C9ORF72* ALS patients were also more likely to be female, have a family history of disease, and had a slightly younger age at onset than the general ALS population [47].

The clinical overlap between ALS and FTLD is pronounced in *C9ORF72* expansion carriers. Patients with ALS and a *C9ORF72* mutation were more likely to have a relative with another neurodegenerative disorder, most commonly FTLD, and approximately 60% of ALS patients with the expansion have a family history of dementia. Dementia was also significantly more common in probands with the *C9ORF72* mutation compared with *SOD1* mutation carriers [56]. These cases more commonly presented with behavioral variant FTLD. Furthermore, over half of FTLD probands with the pathogenic expansion were reported to have a personal or a family history of ALS.

Several studies have identified other neurodegenerative processes in *C9ORF72* carriers, thereby widening the clinical spectrum beyond ALS and FTLD. In a study by Boeve *et al*. [57], parkinsonism was present in approximately one-third of subjects, all of whom had behavioral variant FTLD or ALS-FTLD. Patients with Alzheimer-like amnestic syndromes with prominent hippocampal sclerosis were also identified [52,58]. In a separate study, 38% of patients with *C9ORF72* mutations presented with psychosis, with an additional 28% exhibiting paranoid, deluded or irrational thinking [59]. These findings suggest that the *C9ORF72* expansion may contribute to a broad spectrum of neurodegeneration and psychiatric disorders.

Evidence for incomplete penetrance has been seen in multiple ALS, FTLD, and ALS-FTLD pedigrees. In our own analysis of 604 cases, the pathogenic expansion was non-penetrant in carriers younger than 35 years of age, 50% penetrant by 58 years, and almost fully penetrant by 80 years [49].

Haplotype analysis has suggested that every patient identified to date carrying the pathogenic GGGGCC repeat expansion also shares the Finnish founder risk haplotype, at least in part. Analysis of the haplotype suggests that predisposing or pathogenic hexanucleotide repeat expansion in *C9ORF72* might have occurred on a single occasion in human history 1,500 years ago, and subsequently disseminated throughout the world [39,43,49].

In contrast to this 'single expansion' hypothesis, it is also possible that the *C9ORF72* hexanucleotide repeat is inherently unstable and prone to spontaneous expansion across generations. Under this model, expansions occur on a predisposing haplotype, leading to the occurrence of apparent sporadic cases and anticipation within families with disease. Such a mechanism is known to exist in spinocerebellar ataxia type 8 [60]. Seven-to-ten year anticipation has been noted by several studies in younger generations, and would support this 'recurring event' hypothesis [55,57]. However, proof of this hypothesis will depend on the identification of a pathogenic repeat expansion in an affected offspring that is not present in either parent.

Conclusions: much done, but also much to do

The past year has seen a dramatic growth in our knowledge of the genetics of ALS with the discovery of mutations in *OPTN*, *VCP*, and *UBQLN2*, and the discovery of the repeat expansion in *C9ORF72*. Among them, the *C9ORF72* hexanucleotide expansion is now recognized as the most frequent cause of familial ALS and FTLD, and has shown that genetics plays an important role in sporadic disease. In addition, the *C9ORF72* expansion clearly provides a shared molecular etiology between ALS and FTLD. This discovery is expected to have a large impact on the direction of future research and clinical trials.

Despite this remarkable progress, a number of important questions remain unanswered. First, how many repeats are required for the expansion to precipitate neurodegeneration? Second, does repeat length variation contribute to the age of disease onset, the speed of disease progression, or even drive whether a patient will present with an ALS or FTLD phenotype? Third, do additional factors such as variation within the repeat expansion, variation in local gene expression, or modifiers elsewhere in the genome influence the disease? Fourth, defining the mechanism by which the repeat expansion leads to selective neuronal degeneration is key in understanding the disease, and an essential first step in the development of therapies aimed at modifying disease progression. And finally, what are the genes responsible for the other one-third of familial ALS and the other 90% of sporadic disease? Expanding our knowledge of the genetics of ALS and FTLD is a necessary step to a more complete understanding of the pathogenic pathways underlying these fatal neurodegenerative disorders.

Abbreviations

ALS, amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration.

Competing interests

Bryan Traynor has a patent pending on the diagnostic and therapeutic implications of the *C9ORF72* hexanucleotide expansion discovery.

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Author details

[1]University of California Irvine School of Medicine, Irvine, CA 92697, USA. [2]Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD 20892, USA.

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