HHS Public Access

Author manuscript

Brain Res. Author manuscript; available in PMC 2018 April 25.

Published in final edited form as:

Brain Res. 2015 May 14; 1607: 75–93. doi:10.1016/j.brainres.2014.10.009.

Genetic causes of amyotrophic lateral sclerosis: new genetic analysis methodologies entailing new opportunities and challenges

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Abstract

The genetic architecture of amyotrophic lateral sclerosis (ALS) is being increasingly understood. In this far-reaching review, we examine what is currently known about ALS genetics and how these genes were initially identified. We also discuss the various types of mutations that might underlie this fatal neurodegenerative condition and outline some of the strategies that might be useful in untangling them. These include expansions of short repeat sequences, common and low-frequency genetic variations, *de novo* mutations, epigenetic changes, somatic mutations, epistasis, oligogenic and polygenic hypotheses.

Keywords

Amyotrophic lateral sclerosis; Gene discovery; Genetic heterogeneity; GWAS; NGS; Somatic mosaicism

1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motor neurons leading to rapidly progressive paralysis and eventually death from respiratory failure. Although this core definition is remarkably straightforward, it is becoming increasingly apparent that ALS is not a monolithic entity, but rather represents a heterogeneous group of diseases that share clinical features.

Examples of the heterogeneity associated with ALS are easy to find: the majority of cases die within three to four years of disease onset, but up to 10% of ALS patients survive for

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more than 10 years (Chiò et al., 2009a); there is wide variability in disease from population to population and across geographical region (Cronin et al., 2007); age at onset ranges from early twenties to the ninth decade of life; the clinical manifestation of disease differs from patient to patient in terms of clinical onset (bulbar-onset versus spinal-onset disease, proximal versus distal weakness, upper limb versus lower limb predominant), course (upper motor neuron versus lower motor neuron predominant), and frontotemporal lobe involvement (normal cognition versus mild cognitive impairment and/or dementia), to name but a few. Variability in neuropathology has also been observed with TDP-43 positive inclusions dominating most cases, but other cases lacking these inclusions.

Genetics offers a means to dissect out this heterogeneity and understand the cellular mechanisms leading to motor neuron degeneration. Paradoxically, however, it is this very heterogeneity associated with ALS that is the biggest obstacle to unraveling the genetics. (Singleton et al., 2010)

1.1. What portion of ALS is genetic?

For decades after its initial description in the half of 19th century (Aran, 1848; Cruveilhier 1852; Charcot and Joffroy, 1869), ALS was thought to be a non-hereditary disease. It was not until Kurland and Mulder reported on familial aggregation in the 1950s that heritable factors were considered important in ALS etiology (Kurland and Mulder, 1955). Today, a family history of disease is recognized in 10% of cases, whereas the remaining 90% of cases are labeled as sporadic as they appear to occur randomly in the community. Even here, however, the sands are shifting, with an increasing portion of cases recognized as having a family history of related neurodegenerative diseases such as frontotemporal dementia. Autosomal dominant inheritance is by far the most common, but incomplete penetrance appears to be the rule.

To date, the genetic etiology of approximately two thirds of familial ALS and about 10% of sporadic disease has been identified (Renton et al., 2014). Genetic mutations are clearly responsible for the remaining one third of familial disease, but it is not known how much of the remaining sporadic disease is genetic and how much is due to other factors such as environmental exposures, aging or lifestyle choices? Genome-wide data suggest that genetic factors contribute to at least 23% of sporadic ALS (Keller et al., 2014). Even this high value, however, is likely to be an underestimate as the calculation was based on common variants in the human genome and would not capture the portion of disease arising from rare variants.

To date, more than twenty-five genes linked to ALS have been identified (table 1, figure 1). We present these genes in two categories, namely (a) genes identified using linkage analysis and positional cloning, and (b) genes identified through the application of advanced genome-wide technologies. Though not every gene fits neatly into this framework, describing the genetic discoveries in ALS in this way provides a historical context and highlights how advances in genomic technologies are revolutionizing the way we think about this fatal neurodegenerative disease.

2. GENES IDENTIFIED USING LINKAGE ANALYSIS AND POSITIONAL CLONING

2.1. SOD1

In 1993, an international consortium identified *SOD1* as a gene responsible for autosomal dominant FALS cases, by means of linkage analysis in 18 ALS pedigrees (Rosen et al., 1993). Through this method is possible to map the location of disease-causing loci by testing the co-segregation of genetic markers with the phenotype of interest. Multiple markers across the whole genome are usually screened in large families and a statistical test is performed to determine which markers are inherited by affected subjects more often than would be expected by chance. Candidate regions are eventually studied to identify the causative gene and mutations (posistional cloning). To date, over 150 different mutations have been reported in this gene, consisting primarily of missense mutations, with a smaller number of nonsense and deletion/insertion mutations. Synonymous, intronic and upstream variants are reported, though they are less likely to be pathogenic. *SOD1* mutations can be identified in 12 to 20% of FALS cases and in about 1–2% of apparently sporadic cases (Chiò et al., 2008, Millecamps et al., 2010; Rosen et al., 1993). However, significant differences are observed across ethnic groups (Alavi et al., 2013; Brown et al., 2012; Kwon et al., 2012; Tsai et al., 2013).

It is not clear whether all of the reported variants in *SOD1* are pathogenic, or instead represent incidental findings in affected subjects. Reliable genetic evidence in the form of segregation in large families or their observations in multiple affected subjects, and not in normal individuals matched for ethnicity, exists only for a portion of them (Andersen et al., 2006).

Most *SOD1* mutations show an autosomal dominant, high-penetrance pattern of inheritance. In contrast, recessive inheritance is instead typical for D90A mutation in Scandinavian population (Andersen et al., 1996). Clear genotype-phenotype correlations and prognostic trends can be drawn only for few mutations. A4V, the most common variant in North America, is responsible for an aggressive form of ALS, in which death occurs usually within a year after symptoms onset (Cudkowicz et al., 1997). Other variants consistently associated with a poor survival are G41S, G93A, and R115G. D90A homozygosity is associated with prolonged survival of over 10 years and may present with sensory involvement.

2.2. *TARDBP* (TDP-43), *FUS* and the other RNA-binding genes

Following the discovery of TAR DNA-binding protein 43 (TDP-43) as a major component of ubiquitin-positive cytoplasmic inclusions that are the neuropathological hallmark of the disease (Neumann et al., 2006), mutations in the *TARDBP* gene (encoding the TDP-43 protein) were identified in both sporadic and familial ALS cases (Gitcho et al., 2008; Kabashi et al., 2008; Sreedharan et al., 2008). A total of 47 different missense and one truncating mutations have now been reported (Lattante et al., 2013) and overall *TARDBP* mutations are found in about 4% of FALS cases (Chiò et al., 2008; Millecamps et al., 2010) and about 1% of sporadic cases (Chiò et al., 2008; Brown et al., 2012, Kwon et al., 2012;

Mentula et al. 2012; Tsai et al., 2013). A founder effect may explain the relatively high frequency of the A382T variant in Sardinian population (Chiò et al., 2011a).

In agreement with the fact that TDP-43 inclusions are also typical of FTD, clinical phenotypes associated with *TARDBP* mutations include ALS with cognitive impairment and FTD (Chiò et al. 2010), FTD without ALS (go et al., 2009), and clinically definite Parkinson disease (Quadri et al., 2011; Rayaprolu et al., 2013).

Shortly after the discovery of TARDBP as a cause of familial ALS, mutations were identified in *FUS* within a linkage region on chromosome 16 (Vance et al., 2009; Kwiatkowski et al., 2009). FUS protein shares functional homology with TDP-43, and nearly all the reported mutations in both genes affect the protein C-terminus containing ribonucleoprotein binding domain. Mutations in this gene account for ~5% of FALS and about 1% of SALS, with higher rates observed in oriental populations (Brown et al., 2012; Chiò et al., 2008; Lattante et al. 2012; Millecamps et al., 2010; Tsai et al., 2013; Yan et al., 2010). The associated phenotype is typical ALS, often juvenile onset, though some individuals present with FTD. Most ALS cases carrying a mutation in *FUS* appears to have a peculiar neuropathological signature, in that FUS-immunoreactive cytoplasmic inclusions can be found on autopsy, rather than phosphorylated TDP-43 (Vance et al., 2009; Kwiatkowski et al., 2009).

Both TDP-43 and FUS proteins contain a prion-like domain, a feature that may promote aggregation by acting as a template to induce the misfolding of native proteins and their entrapment into aggregates. Couthouis et al. (2011) performed a systematic survey of human proteins harboring RNA recognition motifs and prion-like domains to find additional candidates similar to TDP-43 and FUS. Among the candidate proteins identified, they performed mutational analysis of TAF15-encoding gene, leading to the identification of missense variants in patients with ALS (Couthouis et al., 2011). Sequencing of *EWSR1*, another gene belonging to the same group, yielded similar results (Couthouis et al., 2012). Definitive confirmation that *TAF15* and *EWSR1* are ALS genes based on segregation within a family is eagerly anticipated.

2.3. Other FALS genes identified through linkage analysis and cloning

For some of the identified genes, observed phenotypes can be more consistently related to different neurological disorders: recessive *ALS2* (Eymard-Pierre et al., 2002; Hadano et al., 2001) and *SPG11* (Daoud et al., 2012) mutations cause hereditary spastic paraplegia, overlapping with juvenile primary lateral sclerosis or juvenile ALS. *SETX* mutations are more typically associated with ataxia (Chen et al., 2004; Duquette et al., 2005). *FIG4* mutations cause autosomal recessive Charcot-Marie-Tooth disease, type 4J, a hereditary motor sensory neuropathy (Campeau et al., 2013; Chow et al., 2009; de Leeuw, 2008).

Optineurin (*OPTN*) mutations have long been described as a cause of primary open angle glaucoma (Reazaie et al., 2002). Recently, both heterozygous and homozygous mutations have been reported in FALS cases (Maruyama et al., 2010), with either dominant or recessive pattern of inheritance. Nonetheless, mutations in this gene appear to be a rare cause of ALS (Sugihara et al., 2011).

A single missense *VAPB* mutation (P56S) was initially identified in several Brazilian families presenting with different phenotypes: atypical ALS, late-onset spinal muscular atrophy, and typical severe ALS with rapid progression (Nishimura et al., 2004). To date, only one other *VAPB* mutation has been described to date in association with ALS (T46I) (Chen et al., 2010).

Following the detection of an association of ALS with the rs11701 SNP in the Irish population, *ANG* was identified as a candidate gene and several mutations have been reported in both FALS and SALS cases (Greenway et al., 2004; Greenway et al., 2006). However, the causal role of *ANG* has not yet been defined and remains ambiguous, since some variants have been repeatedly found in healthy controls, and some *ANG* mutated subjects have been reported bearing mutations in different ALS-causing genes (Luigetti et al., 2011; Lattante et al., 2012).

UBQLN2 is the only ALS gene mapping on chromosome X identified to date (Deng et al., 2011). Even though *UBQLN2* mutations are a rare cause of ALS, its role in the pathogenesis of ALS is supported by the observation that ubiquilin-2 is a component of skein-like inclusions that are considered a hallmark of ALS pathology.

The p62/sequestosome 1 protein is another component of pathological inclusions in neurodegentative diseases, including ALS. Based on these findings, sequencing analysis of the p62-encoding gene, *SQSTM1*, allowed for the detection of mutations in ALS patients, but also in cases with ALS-FTD and isolated FTD. According to various reports, *SQSTM1* variants may account for 1–2% of FALS and up to 4% of SALS (Chen et al., 2014; Fecto et al., 2011; Kwok et al., 2014; Rubino et al., 2012; Teyssou et al., 2013).

CHMP2B is another gene whose involvement in ALS was found through a candidate gene approach, supported by the initial discovery of a mutation in an FTD family (Parkinson et al., 2006). *CHMP2B* mutations have been found in very few ALS cases, but they seem to be more specifically associated with the lower motor neuron predominant variant of ALS (with a detection rate of about 10%) (Cox et al., 2010).

Other genes claimed to be involved in ALS are the following: *HFE* (Goodall et al., 2005; Li et al., 2014); *VEGF* (Lambrechts et al., 2009); *NEFH* (Al-Chalabi et al., 1999, Figlewicz et al., 1994) and *PRPH* (Corrado et al., 2011; Leung et al., 2004; Gros-Louis et al., 2004), both coding for intermediate filament proteins; the paraoxonase genes *PON1*, *PON2* and *PON3* (Wills et al., 2009); *DCTN1* (Puls et al., 2003; Münch et al., 2004), whose mutations are now more commonly linked to Perry syndrome (Farrer et al. 2009); *SIGMAR1* and genes coding for the subunits of acetylcholine receptors, mainly *CHRNA4* (Sabatelli et al., 2009; Sabatelli et al., 2012a); *SIGMAR1* (Al-Saif et al., 2011) and *ERLIN2* (Al-Saif et al., 2012), are repored to be responsible for juvenile ALS and juvenile primary lateral sclerosis.

2.4. Validation of ALS causative variants

Several genes have been claimed to be someway related to ALS in scientific literature (see table 1). Even if there is consensus about the causal role of a subset of major genes like *C9orf72, SOD1*, *TARDBP*, and *FUS*, for other genes further evidences are required.

It is worth noting that concerns have been raised even regarding the actual pathogenicity of a small number of *SOD1* mutations (Felbecker et al. 2010).

It is actually a tough task to provide definitive proof of pathogenicity for ALS-associated variants. The co-segregation of a specific variant with the disease in large families and the presence of the same variant in multiple unrelated patients and not in control subjects are usually considered as self-conclusive evidence, but they can be applied only to a limited number of cases. Functional studies provide insight into pathophysiological mechanisms, but extreme caution should be applied in using functional biological data to support weak genetic data.

Locus and allelic heterogeneity of ALS are the main factors complicating the discovery and validation of ALS genetics, since a single gene may be involved in a very limited number of cases. Furthermore, the relative impact of various genes may be significantly diverse among different populations.

A subset of genes reported to be mutated in ALS patients are primarily known to be responsible for different neurological conditions (e.g.: *ALS2, VAPB, SPG11, FIG4, ATXN2, SPAST, DCTN1, SMN1*).

Some variants initially detected in ALS patients were subsequently found to be present in healthy controls (e.g.: *ANG* gene). This highlights the importance of keeping an open mind with respect to reported mutations and a willingness to revise previous closely held opinions of pathogenicity.

Finally, some variants might not be responsible for ALS by themselves, but they could act as predisposing or disease-modifying factors.

3. GENES IDENTIFIED THROUGH THE APPLICATION OF ADVANCED GENOME-WIDE TECHNOLOGIES

3.1. Genome-wide association studies of ALS

Association studies involve comparison of the frequencies of genetic variants between groups of unrelated affected individuals and control subjects. Initial association studies were based on a candidate gene approach, but, with advances in genomic assay technology, several million markers across the genome can now be interrogated in a single experiment. This is known as genome-wide association study (GWAS).

Several GWAS have been published in ALS (Schymick et al., 2007; van Es et al., 2007; Cronin et al., 2008a; van Es et al., 2008; Simpson et al., 2009; Chiò et al., 2009b; Landers et al., 2009; van Es et al., 2009; Laaksovirta et al. 2010; Shatunov et al., 2010; Iida et al., 2011; Kwee et al., 2012; ALSGEN Consortium et al., 2013; Deng et al., 2013; Fogh et al. 2014). In addition, there have been studies of copy number variation (Blauw et al., 2008; Cronin et al., 2008; Wain et al., 2009; Blauw et al., 2010; Uyan et al. 2013), a study specifically focusing on homozygosity segments (Mok et al. 2013), and a pooling GWAS combined with pathway analysis (Xie et al., 2014).

A role as a risk factor has been invoked for several loci, including *FGGY* (Dunkley et al., 2007) , *DPP6* (Van Es et al., 2008), *ELP3* (Simpson et al., 2009), *UNC13A* (van Es et al., 2009; Shatunov et al., 2010), *ZNF512B* (Iida et al. 2011), *ITPR2* and *SUNC1* (Chiò et al., 2009b). For most of them, significant associations were not confirmed in subsequent replication studies.

Several factors may be invoked to explain why many of the GWAS hits have not replicated. Most ALS causative variants are limited to very small number of patients. Consequently, there are population stratification issues that are not easily eliminated: GWAS signals may be driven up by very few samples that cannot be significantly represented in different study cohorts. Furthermore, false positive results should always be considered even in presence of statistical significance. These effects are even more likely for small case-control cohorts, as they were in older GWAS studies.

For these reasons, the main goal remains the identification of the actual pathogenic variant: in fact, the most important result obtained by GWAS remains the definition of the *C9orf72* locus (see section 3.4).

Genome-wide association studies can be adapted to look for genetic variants that modify phenotype, for example age at symptom onset or prognosis. Among others, *PGRN* (Sleegers et al., 2008), *KIFAP3* (Landers et al., 2009), *EPHA4* (Van Hoecke et al., 2012), *UNC13A* (Chiò et al., 2013; Diekstra et al., 2012a), *ZNF512B* (Tetsuka et al., 2013), *PPARGC1A* (Eschbach et al., 2013) have been reported to influence the survival in ALS, while *PGRN*, *PPARGC1A*, *APOE* (Zetterberg et al., 2008) *MAO*-B (Orrù et al., 1999) have been proposed as modifier of age of onset. These associations should be intrepted cautiously, as they still need confirmation and attempts to replicate the observed effects in some cases led to conflicting results (Traynor et al., 2010).

Genetic and allelic heterogeneity are the most important confounding factors for GWAS, since the presence of multiple risk haplotypes reduces the intensity and significance of detected signals. Clearly, this is the case for ALS that is increasingly recognized to represent a collection of similar neurological diseases rather than a single nosological entity. Future GWAS will need to be designed to maximize the statistical power and minimize the false discovery rate: this will involve larger case-control cohorts, as well as stratification of GWAS data based on different populations and well-defined clinical categories. Furthermore, newer generations of GWAS platforms assay rare variants with potentially larger effects on phenotype.

3.2. Copy number variants

Copy number variants constitute an important source of human genetic variability. They mainly consist of the loss (deletion) or gain (duplication) of stretches of DNA sequence, typically 1 kb to several Mbs in size. Similar to single nucleotide polymorphisms (SNPs), copy number variants are detected in healthy people. Several surveys have been performed in attempt to evaluate the involvement of copy number variants in ALS (Blauw et al., 2008; Cronin et al., 2008; Wain et al., 2009; Soichet et al., 2009; Blauw et al., 2010; Uyan et al. 2013), while others investigated specific categories of copy number variants including *de*

novo copy number variants (Pamphlett and Morahan, 2011a), somatic copy number variants (Pamphlett and Morahan, 2011b; Pamphlett and Morahan, 2011c), and copy number variants in ALS-discordant monozygotic twin pairs (Pamphlett and Morahan, 2011c). Although many copy number variants that were specific to patients with ALS were detected, common copy number variants were not significantly associated to ALS in these studies.

Homozygous deletions of *SMN1* underlie the most common cause of spinal muscular atrophy and several studies have suggested that duplication of *SMN1* gene may contribute to ALS susceptibility (Wang et al., 2014, Kuzma-Kozakiewicz et al., 2013; Blauw et al., 2012; Corcia et al., 2002; Corcia et al.; 2006). Conflicting results have been obtained for *SMN2*, a homologe of *SMN1* (Lee et al., 2012a; Corcia et al., 2012). Finally, a recent study pointed out that deletion of *EPHA3* might be a protective factor (Uyan et al., 2013). Taken together, these data indicate that the role of copy number variants in ALS has not been fully resolved and is worth exploring further, possibly with the help of newer genome-wide technologies.

3.3. Next generation sequencing

The recent introduction of high-throughput massive parallel sequencing methods has revolutionized gene-hunting strategies. Whole-exome sequencing allows the identification of coding variants across (nearly) all genes (the so-called “exome”). In so doing, this type of genetic analysis facilitates the rapid identification of pathogenic mutations and is ideally suited to the study of families for which a limited number of samples are available.

By applying WES to a four-generation family with four members presenting with autosomal dominantly inherited ALS, a missense mutation in *VCP* gene was found segregating with the disease (Johnson et al., 2010). This finding was supported by the identification of other *VCP* mutations in FALS and SALS cases (Koppers et al., 2012; Abramzon et al., 2012). The causal role of VCP was further strengthened by the fact that it was already known to underlie a syndromic condition characterized by FTD, inclusion body myopathy and Paget’s disease of the bone (IBMPFD). The same approach more recently led to the discovery of mutations in *HNRNPA1* and *HNRNPA2B1* (Kim et al., 2013).

These recent genetic findings arising from exome sequencing have expanded our understanding of the pleiotropic effects and phenotypic spectrum associated with specific genes. Several kindreds have now been described in which apparently unrelated manifestations involving different organs and systems are observed: Paget’s disease of bone, inclusion body myopathy, and lastly ALS and FTD. The term “multisystem proteinopathy” has been proposed to describe these diverse, but somehow interconnected conditions, based on their shared pathologic features of protein aggregation in affected tissues (Benatar et al., 2013). Four genes have been identified whose mutations are likely responsible for that multifaceted syndrome, *VCP*, *SQSTM1*, *HNRNPA2B1* and *HNRNPA1*, and even though their relative involvement in ALS appears to be limited, their discovery sheds new light on pathogenic mechanisms underlying ALS.

Another gene whose mutations were identified by means of WES in large ALS kindreds is *PFN1* (Wu et al., 2012). More recently, mutations in another RNA/DNA binding protein, MATR3, have been reported as a cause of familial ALS in several large kindreds. MATR3

binds directly to TDP-43 and at least some of the identified mutations alter this binding in a selective and RNA-dependent manner (Johnson et al., 2014). Overall, this provides further support for the notion that disruption of RNA metabolism is central to motor neuron degeneration.

The last identified gene is *CHCHD10*, whose mutations may be responsible for ALS alone (Müller et al. 2014) or in association with frontotemporal dementia, cerebellar ataxia and myopathy (Bannwarth et al., 2014; Chaussenot et al., 2014; Johnson et al., 2014). It appears to be involved in mitochondrial stability and its discovery breathes new life into long-standing theories suggesting an important role played by mitochondrial dysfunction in ALS pathogenesis (Cozzolino et al., 2013). Other *CHCHD10* mutations were reported to be responsible for autosomal dominant mitochondrial myopathy (Ajroud-Driss et al., 2014).

3.4. *C9orf72* repeat expansion

The identification of the GGGGCC-repeat expansion in the first intron of *C9orf72* as the cause of 9p21-linked ALS and FTD (Renton et al., 2011; DeJesus-Henrnandez et al., 2011) was the result of the application of both linkage analysis (Pearson et al., 2011; Morita et al., 2006; Le Ber et al., 2009), GWAS (van Es et al., 2009; Shatunov et al., 2010; Laaksovirta et al., 2010) and next generation sequencing. The *C9orf72* repeat expansion constitutes the most frequent genetic cause of both FALS (about 40 %) (Majounie et al., 2012; Chiò et al., 2012a) and SALS cases (about 7 %) (Sabatelli et al., 2012b), providing the definitive evidence that the same etiopathogenic mechanisms underlie both SALS and FALS. The expansion also accounts for a remarkable percentage of familial FTD cases (about 25 %) (Majounie et al., 2012), thus consolidating the concept that ALS and FTD are different manifestations of a common neurodegenerative pathway. It is worth noting that the reported rates of *C9orf72* expansion are referred to populations of European descent and lower rates have been observed in different ethnic groups (Alavi et al., 2014; Ogaki et al., 2012; Zou et al., 2013a).

The understanding of the molecular mechanisms underlying the pathogenesis of *C9orf72*-related ALS is important not only for its prognostic and therapeutic implications, but also because it can help the further discovery of other ALS causative factors. For example, urged by these findings, scientist have been searching for other repeat-expansion in ALS, *ATXN2* CAG-repeat expansions are associated with increased risk of developing ALS (Liu et al., 2013; Daoud et al., 2011; Van Damme et al., 2011; Elden et al., 2010). Conversely, the analysis of the nucleotide repeat lengths of genes associated with other neurologic or neuromuscular disorders revealed no association with ALS (Groen et al., 2012; Figley et al., 2014).

3.5. *De novo* mutations

De novo mutations have been reported to play an important role in the pathogenesis of many disorders, such as autism and schizophrenia (Epi4K Consortium et al., 2013; Gratten et al., 2013; Neale et al., 2012; Sanders et al., 2012; Vissers et al., 2013; Xu et al. 2011) and also have been identified in known ALS genes (Alexander et al., 2002; Zou et al., 2013b; Calvo et al., 2014; Conte et al., 2012; Chiò et al. 2011b; DeJesus-Hernandez et al., 2010). The

power of applying exome-sequencing to parents-case offspring trios is that it allow the investigator to look for *de novo* mutations across the genome and not just confined to known ALS genes. To this end, an exome sequencing study involving 47 ALS patient-parents trios identified *CREST* as a new gene possibly involved in ALS (Chesi et al., 2013). However, each individual in the general population carries up to four *de novo* coding mutations, meaning that identification of a *de novo* variant in a gene does not constitute proof of its pathogenicity. Additional genetic data are required to validate that mutations in the nominated gene are truly causative, something that is lacking in current publications.

4. FURTHER GENETIC MECHANISMS/ANALYSES YET TO BE FULLY EXPLORED

4.1 Epigenetics

Epigenetic modifications influence the expression pattern of the genome, Alteration of epigenetic processes, including DNA methylation, have been long known as causes of human diseases (e.g. imprinting syndromes, conditions caused by mutation in genes regulating epigenetic modifications, and cancer). Epigenetic mechanisms also appear to be involved in motor neuron cell death (Chestnut et al. 2011). Furthermore, epigenetics changes are the consequence of a dynamic process influenced by the interaction between genes and environment, and a fraction of those changes might even be transmitted to the offspring (Gu et al., 2012).

Genome-wide analyses have been performed to date in ALS investigating epigenetic changes or differences in epigenetic signature (i.e.: DNA-methylation pattern) between patients and controls (Morahan et al., 2009; Figueroa-Romero et al., 2012). Despite statistically significant results, suggesting epigenetically altered genes in ALS, confirmatory evidences are still pending.

4.2 Oligogenic and polygenic models of ALS

Interaction of multiple risk variants at different loci in single individuals is an important aspect to consider when dissecting the genetics bases of a complex disease such as ALS. The fact that mutations in ALS causative genes display a classic Mendelian pattern of inheritance may lead to the belief that ALS is a monogenic disorder. Nevertheless, a significant part of ALS heritability cannot be easily explained by only considering a simple monogenic model (Singleton et al., 2010). Identification of epistatic interactions among multiple ALS-related genes might explain the substantial phenotypic differences observed among subjects carrying identical mutations and the incomplete penetrance observed in some families.

Supporting an oligogenic basis of ALS, there are reports of the co-occurrence of mutations in two ALS-related genes (i.e.: *C9orf72*, *SOD1*, *FUS*, *TARDBP*, and *ANG*) in both isolated patients and multiple individuals from ALS families (Luigetti et al., 2011; van Blitterswijk et al., 2012; Chiò et al., 2012b). Compound inheritance of two variants with different effect sizes and frequencies (i.e.: a high risk rare mutation and a more frequent allele acting as a modifier) in the same ALS gene might account for incomplete penetrance observed in ALS families, as already demonstrated in a different genetic condition (Albers et al., 2011).

4.3 Somatic mutations

Somatic mutations are a well-known cause of human disease, with cancer being the most striking example. Advances in next generation sequencing has allowed the discovery of mutations involving a small fraction of brain cells as a cause of severe neurological disorders (Rivière et al, 2012; Lee et al., 2012; Poduri et al., 2012). Several studies also show that mosaicism is a feature of “normal” brain (McConnell et al., 2012; Bushman et al., 2013; Baillie et al., 2011). These observations support the hypothesis that brain mosaicism may be a cause of some complex neurological and psychiatric diseases. Due to cortical architecture and developmental processes, it is also possible that neurons carrying a mosaic mutation are not clustered together, but are interspersed with “normal” neurons (Poduri et al., 2013). For example, a mosaic mutation may involve pyramidal neurons throughout the cortex, sparing all the other types of cortical neurons and glial cells. It is worth citing a reported case of sporadic, early onset Alzheimer’s disease attributed to a somatic presenilin-1 mutation in brain cells (Beck et al., 2004) and a case of Creutzfeld-Jacob disease caused by an early embryonic somatic mutation in *PRNP* gene (Alzualde et al., 2010). To our knowledge, no such an example has yet been described in ALS, but it remains an interesting hypothesis to be tested in the next future. Furthermore, prion-like mechanisms have been proposed in ALS pathogenesis (Grad et al., 2011; Munch et al., 2011; Furukawa et al., 2011; Nonaka et al., 2013) and, at least conceptually, mosaic mutations would fit with that notion.

7. UNRAVELING THE GENETICS OF ALS: THE WAY FORWARD

Recent years has seen a boom in the identification of new ALS genes. The discovery of the *C9orf72* repeat expansion had the biggest impact, explaining a significant proportion of both FALS and SALS cases and of the observed overlap between ALS and FTD. It has been argued that are unlikely to be other genetic discoveries with as high a frequency as the C9orf72 mutation and that, given the high cost of genetic studies, the ALS research community should focus their efforts elsewhere. Perhaps not unsurprisingly, we disagree with that sentiment and counter that a more complete knowledge of the underlying genetic defects is essential in studying and understanding pathogenic mechanisms leading to ALS. Furthermore, frequency should not necessarily be taken as a barometer of importance. For example, mutations in the *TARDBP* gene account for barely 4% of familial ALS cases, and yet the presence of TDP-43 pathology has come to define the disease.

This leaves us with the question as to how to move forward in the increasingly complicated ALS genetic space. Key to this will be larger cohorts of cases and controls and this will necessitate national and international collaboration to collect these samples. In that regard, making raw genomic data publicly available is an important component, as it allows researchers around the world to access the data and combine it with their own results, thereby increasing the power of their dataset for free. The infrastructure for this socially conscious data sharing has already been established in the form of the dbGaP repository (www. http://www.ncbi.nlm.nih.gov).

The discovery of new genes is in some ways a self-sustaining process: it facilitates further discoveries through many procedures. The characterization of the genetic defects underlying ALS will help to define nosologically the multifaceted nature of ALS as a spectrum of

disease, allowing for a classification of cases into clearer phenotypically categories, in which a common genetic cause is more likely to be identified: the “overlapping phenotype” strategy has already demonstrated to be effective in studies relying on WES (Gilissen et al., 2012). A more precise stratification of ALS patients based on the presence of causative genetic mutations will help the identification of further genetic variants acting as modifiers of the phenotype. Similarly, studies aimed to define environmental risk factor will largely benefit form a better characterization of the genetic background.

Finally, but most importantly, the identification of the genetic etiology of ALS allows for the development of targeted therapeutic interventions. Gene therapy in the form of personalized medicine holds great promise and already early stage clinical trials involving antisense oligonucleotides against mutated SOD1 have been completed (Miller et al., 2013). Similar therapy has been proposed also for the *C9orf72* repeat expansion (Fernandes et al., 2013).

List of abbreviations

ALS	Amyotrophic lateral sclerosis
FALS	Familial amyotrophic lateral sclerosis
SALS	Sporadic amyotrophic lateral sclerosis
FTD	Frontotemporal dementia
GWAS	Genome-wide association study
SNP	Single-nucleotide polymorphism
NGS	Next generation sequencing
WES	Whole exome sequencing
dbGaP	database of Genotypes and Phenotypes
OMIM	Online Mendelian Inheritance in Man

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Highlights

- Amyotrophic lateral sclerosis constitutes a heterogeneous neurodegenerative disorder
- Genetics factors play a significant role in ALS etiology and pathogenesis
- Genetic causes of ~65% of familial and ~10% of sporadic ALS have been identified
- Different genetic mechanisms underlie ALS etiology
- NGS techniques may favor the discovery of new genes

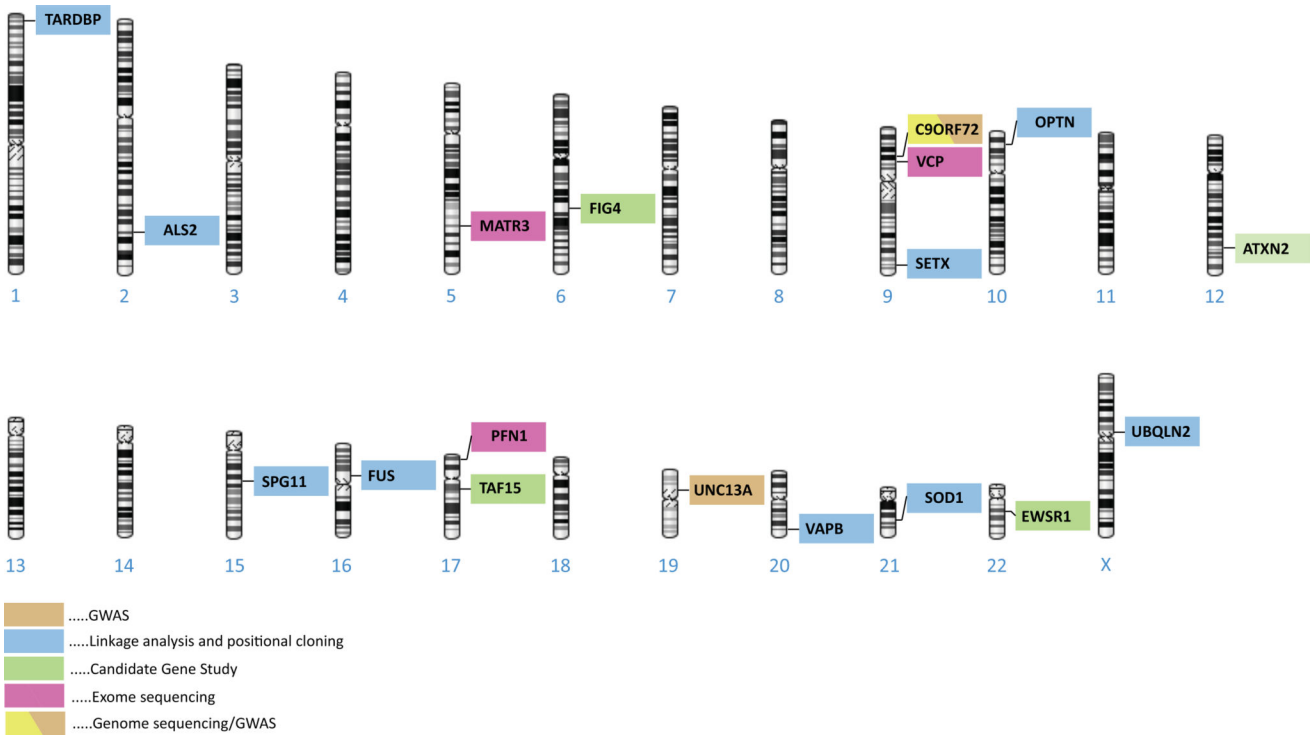

Figure 1.
schematic representation of selected ALS genes.

Table 1

list of genes claimed to be involved in ALS etiology and pathogenesis

Gene	Location	FALS locus	Strategy	Suggested role in ALS*	Associated phenotypes	OMIM nr	Refs
SOD1	21q22.11	ALS 1	Linkage analysis	AD, AR, main gene	-	147450	Rosen et al., 1993
ALS2	2q33.2	ALS 2	Linkage analysis	AR, main gene?	Hereditary spastic paraplegia	606352	Hadano et al., 2001
Unknown	18q21	ALS 3	Linkage analysis	AD?	?	(606640)	Hand et al., 2002
SETX	9q34.13	ALS 4	Linkage analysis	AR, main gene?	Spinocerebellar ataxia	608465	Chen et al., 2004
SPG11	15q21.1	ALS 5	Linkage analysis, family study, candidate gene, WES	AR, main gene?	Hereditary spastic paraplegia	610844	Orlacchio et al., 2010; Daoud et al., 2012
FUS	16p11.2	ALS 6	Linkage analysis, candidate gene	AD, AR, main gene	-	137070	Vance et al., 2009; Kwiatkowski et al., 2009
Unknown	20p13	ALS 7	Linkage analysis	AD?	?	(608031)	Sapp et al., 2003
VAPB	20q13.33	ALS 8	Linkage analysis	AD, main gene?	Spinal muscular atrophy, late-onset	605704	Nishimura et al., 2004
ANG	14q11.1	ALS 9	Candidate gene, association study	AD?, main gene? modifier gene?	-	105850	Greenway et al., 2006
TARDBP	1p36.22	ALS 10	Linkage analysis, candidate gene	AD, main gene	FTD	605078	Gitcho et al., 2008; Kabashi et al., 2008; Sreedharan et al., 2008
FIG4	6q21	ALS 11	Candidate gene	AD, AR, main gene?	Charcot-Marie-Tooth disease, type 4J; Yunis-Varon syndrome	609390	Chow et al., 2009
OPTN	10p13	ALS 12	Family study: homozygosity mapping	AD, AR, main gene	Open angle glaucoma	602432	Maruyama et al., 2010
ATXN2	12q24.12	ALS 13	Candidate gene	Susceptibility gene	Spinocerebellar ataxia	601517	Elden et al., 2010; Daoud et al., 2011
VCP	9p13.3	ALS 14	Family study: WES	AD, main gene	FTD, inclusion body myopathy, Paget's disease	601023	Johnson et al., 2010
UBQLN2	Xp11.21	ALS 15	Linkage analysis	XL, main gene	FTD	300264	Deng et al., 2011
SIGMAR1	9p13.3	ALS 16	Family study: homozygosity mapping	AR, main gene	-	601978	Al-Saif et al., 2011
CHMP2B	3p11.2	ALS 17 (ALS-FTD3)	Linkage analysis, candidate gene	AD, main gene	FTD	609512	Parkinson et al., 2006
PFN1	17p13.3	ALS 18	Family study: WES	AD, main gene	-	176610	Wu et al., 2012
Unknown	9q21-q22	ALS-FTD 1	Linkage analysis	AD?	FTD		Hosler et al.,, 2000

Gene	Location	FALS locus	Strategy	Suggested role in ALS*	Associated phenotypes	OMIM nr	Refs
C9orf72	9p21.2	ASL-FTD 2	GWAS, linkage analysis	AD, main gene	FTD	614260	Renton et al., 2011; DeJesus-Henmandez et al., 2011
MATR3	5q31.2		Family study: WES	AD, main gene	-	164015	Johnson et al., 2014
CHCHD10	22q11.23		Family study: WES	AD, main gene	FTD, cerebellar ataxia, myopathy	615903	Bannwarth et al., 2014; Chaussenot et al., 2014
SQSTM1	5q35.3		Candidate gene	AD, main gene	FTD, inclusion body myopathy, Paget's disease	601530	Fecto et al., 2011
TAF15	17q12		Candidate gene	AD, main gene?	-	601574	Couthouis et al., 2011
EWSR1	22q12.2		Candidate gene	AD?, main gene?	-	133450	Couthouis et al., 2012
HNRNPA1	12q13.13		Family study, WES	AD, main gene	FTD, inclusion body myopathy, Paget's disease	164017	Kim et al., 2013
HNRNPA2B1	7p15.2		Family study, WES	AD, main gene	FTD, inclusion body myopathy, Paget's disease	600124	Kim et al., 2013
SPAST	2q22.3		Candidate gene	AD, main gene?	Hereditary spastic paraplegia	604277	Meyer et al., 2005
VEGF	6p21.1		Candidate gene, association study	Susceptibility gene	-	192240	Lambrechts et al., 2009
HFE	6p22.2		Candidate gene, association study	Susceptibility gene	Hemochromatosis	613609	Goodall et al., 2005
NEFH	22q12.2		Candidate gene, association study	Susceptibility gene?	-	162230	Al-Chalabi et al., 1999; Figlewicz et al., 1994
PRPH	12q13.12		Candidate gene	AD?, main gene?	-	170710	Leung et al., 2004
PON1, 2, 3	7q21.3		Candidate gene, association study	Susceptibility gene?	-	168820	Wills et al., 2009
DCTN1	2p13.1		Linkage analysis	AD, main gene?	Perry syndrome	601143	Puls et al., 2003
CHRNA4	20q13.33		Candidate gene, association study	Susceptibility gene	Nocturnal frontal lobe epilepsy	118504	Sabatelli et al., 2012
CHRNA3 CHRNB4	15q25.1		Candidate gene, association study	Susceptibility gene?	-	118509 118503	Sabatelli et al., 2009
ERLIN2	8p11.23		Family study: homozygosity mapping	AR, main gene	Hereditary spastic paraplegia	611605	Al-Saif et al., 2012
UNC13A	19p13.11		GWAS	Susceptibility gene, modifier gene	-	609894	Chiò et al., 2013a; Diekstra et al., 2012a
DPP6	7q36.2		GWAS	Susceptibility gene?	Ventricular fibrillation	126141	Van Es et al., 2008
ELP3	8p21.1		GWAS	Susceptibility gene?	-	612722	Simpson et al., 2009

Gene	Location	FALS locus	Strategy	Suggested role in ALS*	Associated phenotypes	OMIM nr	Refs
ZNF512B	20q13.33		GWAS	Susceptibility gene, modifier gene	-	-	Iida et al. 2011; Tetsuka et al., 2013
ITPR2	12p12.1		GWAS	Susceptibility gene?	-	600144	Chiò et al., 2009b
FGGY	1p32.1		GWAS	Susceptibility gene?	-	-	Chiò et al., 2009b
CHGB	20p12.3		Candidate gene, association study	Susceptibility gene?	-	118920	Gros-Louis et al., 2009
DPYSL3	5q32		Candidate gene, association study	Susceptibility gene?	-	601168	Blasco et al., 2013
GRN	17q21.31		Candidate gene, association study	Susceptibility gene, modifier gene	-	138945	Sleegers et al., 2008
KIFAP3	1q24.2		GWAS	Modifier gene	-	601836	Landers et al., 2009
EPHA4	2q36.1		Candidate gene	Modifier gene	-	602188	Van Hoecke et al., 2012
PPARGC1A	4p15.2		Candidate gene, association study	Modifier gene	-	604517	Eschbach et al., 2013
APOE	19q13.32		Candidate gene, association study	Modifier gene	Alzheimer disease	107741	Zetterberg et al., 2008
MAOB	Xp11.3		Candidate gene, association study	Modifier gene	-	309860	Orrù et al., 1999
CX3CR1	3p22.2		Candidate gene, association study	Modifier gene	-	601470	Lopez-Lopez et al., 2014
SMN1 (SMN2)	5q13.2		Candidate gene, association study	Susceptibility gene	Spinal muscular atrophy	600354	Corcia et al., 2002
EPHA3	1q22		GWAS	Protective factor	-	601381	Uyan et al., 2013
SS18L1	20q13.33		WES (trios study)	AD, main gene	-	606472	Chesi et al., 2013
DAO	13q33.2		Linkage analysis	AD, main gene?	-	124050	Mitchell et al., 2010
PNPLA6	19p13.2		Family study: homozygosity mapping	AR, main gene?	Hereditary spastic paraplegia, Boucher-Neuhäuser and Gordon Holmes syndromes	603197	Rainier et al., 2008
MAPT	17q21.31		Candidate gene, association study	Susceptibility gene	FTD	157140	Fang et al., 2013
TREM2	6p21.1		Candidate gene, association study	Susceptibility gene	Alzheimer disease	605086	Cady et al., 2014

GWAS: genome wide association study; WES: whole exome sequencing

AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; X-linked inheritance

OMIM: Online Mendelian Inheritance in Men database (www.omim.org)