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Review

Dissection of genetic factors associated with amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal late onset neurological disorder characterized by motor neuron degeneration in the primary motor cortex, brainstem and spinal cord. The majority of cases are sporadic (SALS) and only 5–10% have a family history (FALS). FALS cases show a high heritability and this has enabled the identification of several genetic triggers, of which mutations in *SOD1*, *FUS*, *TARDBP* and *C9ORF72* are the most frequent. While such advances have contributed to our current understanding of the causes of most cases of FALS and their underlying pathophysiological consequences, they only explain a small fraction of SALS with the etiology of most SALS cases remaining unexplained. Here, we review past and current methods used for the identification of FALS and SALS associated genes and propose a risk-based classification for these. We also discuss how the growing number of whole exome/genome sequencing datasets prepared from SALS cases, and control individuals, may reveal novel insights into the genetic etiology of SALS; for instance through revealing increased mutation burden rates across genes or genomic regions that were not previously associated with ALS or through allowing the examination of a potential "oligogenic" mechanism of the disease. Finally we summarize the three most recently discovered 'high risk' genes in ALS.

Contents

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Introduction

The term "*amyotrophic lateral sclerosis*" was coined by the French neurologist *Jean-Martin Charcot* in the 1800s when he wrote a detailed clinical and pathological description of this disease. "*Amyotrophic*" means muscular atrophy, and, "*lateral sclerosis*" describes the scarring or hardening tissues in the lateral spinal cord. More precisely, the major neuropathological features of ALS are: (1) degeneration of the corticospinal tract, which contains axons projecting from the primary motor cortex to the motor neurons, and extensive loss of lower motor neurons from the anterior horns of the spinal cord (SC) and brainstem (Ghatak et al., 1986; Hughes, 1982); (2) degeneration and loss of Betz cells (large pyramidal cell neurons) in the primary motor cortex, which project their axons to the lower motor neurons *via* the corticospinal tract (Hammer et al., 1979; Maekawa et al., 2004; Udaka et al., 1986); (3) and reactive gliosis, which corresponds to hypertrophy of glial cells (with either a loss of their neuroprotective ability or a gain of neurotoxic effects) in the motor cortex and SC around the areas of degeneration (Ekblom et al., 1994; Kawamata et al., 1992; Murayama et al., 1991; Schiffer et al., 1996). ALS typically starts focally, in a particular segment of the body; either an upper limb or a lower limb (spinal form) or the bulbar region. After the focal initiation, which is usually asymmetric, symptoms spread to other regions over time and some evidence suggests that the spread may be mediated by non-cell autonomous propagation or "prion-like propagation" (Kanouchi et al., 2012). A common feature of many neurodegenerative diseases, including ALS, is the formation of protein aggregates/inclusions in degenerating motor neurons. It is noteworthy that, even though these pathological structures were first observed several decades ago, their presence still remains a topic of considerable debate and they have been independently proposed to be toxic, harmless, or even protective. The exact composition of these protein structures remains largely unknown but the seminal observation of cytoplasmic inclusions containing TDP-43 (TAR-DNA binding protein 43) (Arai et al., 2006; Neumann et al., 2006) or FUS (fused in sarcoma) (Ling et al., 2010) has now become hallmark pathological features of the disease (TDP-43$^+$ for most cases and FUS$^+$ for a small subset of cases). So far, most studies have shown TDP-43 and FUS pathologies to be mutually exclusive, thereby implying independent pathways (Neumann et al., 2009; Seelaar et al., 2010; Vance et al., 2009). Nonetheless, the possibility of interactions between TDP-43 and FUS, as well as their association with other ALS associated proteins, is now an open field of investigation (Mackenzie et al., 2010). Interestingly, the neuronal distribution and prion-like propagation of phosphorylated TDP-43 inclusions now enable pathologist to distinguish four neuropathological stages for ALS (Brettschneider et al., 2013). Up to 50% of ALS patients may also have symptoms and signs of frontotemporal dementia (FTD) with degeneration in the frontotemporal regions of the brain (Liscic et al., 2008). ALS is almost always a fatal disease with progressive muscular weakness and atrophy followed by progressive muscular paralysis, which commonly leads to death through respiratory failure. While significant advances have been made in palliative therapies, there is no cure or means to significantly slow disease progression. Indeed, currently only one CADTH/FDA-approved therapy exists (*Riluzole*) which only offers a modest slowing of disease progression. The aim of this review is to outline the genetic methodologies used to identify loci and genes associated with ALS, and to decipher the genetic factors involved in this disease.

Epidemiology of ALS

ALS is a rare disease with a mean incidence of 2.8/100,000 in Europe and 1.8/100,000 in North America, and a mean prevalence of 5.40/100,000 in Europe and 3.40/100,000 in North America (Chio et al., 2013a). Men are slightly more frequently affected than women with a male:female incidence rate ratio of 1.4 (Logroscino et al., 2010). The median survival period following onset is independent of gender and is usually 2–4 years (Chio et al., 2009a). In most cases, disease onset is during late-adulthood, but juvenile (prior to 25 years) and "young-onset" ALS cases (prior to 45 years), respectively represent ~1% and ~10% of all cases (Logroscino et al., 2010; Turner et al., 2012). In a recent global epidemiological analysis of ALS combining 37 studies, the mean ± SD age for typical ALS disease onset (adult-onset) was estimated at 61.8 ± 3.8 years (range 54–67 years) and mean ± SD age for ALS diagnosis at 64.4 ± 2.9 years (range 58–68 years) (Chio et al., 2013a).

Emergence of genetic susceptibility

The idea of genetic factors being involved in ALS first emerged in 1850 with the publication of several reports highlighting cases with a familial or hereditary history (Strong et al., 1991). Over the past decades it has recurrently been stated that the fraction of ALS cases with a family history, which are often referred to as FALS, is approximately 10%. However, a recent meta-analysis made to establish the rate of FALS using prospective population based registries has indicated that it is lower at 5.1% (confidence interval (CI) 4.1 to 6.1%) (Byrne et al., 2011). There is no definitive criterion for FALS but the general consensus is that "*the presence of ALS in either a first or second degree relative of the index case constitutes the familial form of the disease*". ALS cases with no known family history are referred to as SALS; it is likely that the proportion of SALS cases is an over-estimate because of missing or non-queried information on family history. Familial aggregation studies pooling siblings and children of ALS patients together have shown that the relative risk among the first degree relatives of ALS probands (index case) compared to the reference group is 9.7 (95% CI = 7.2–12.8) and that this relative risk is significantly increased if the proband was diagnosed at a younger age (Fang et al., 2009). In SALS, the risk for ALS among first-degree relatives has been estimated in retrospective parent–offspring studies to be around 1% (Hanby et al., 2011; Wingo et al., 2011). Twin studies based on 171 twin pairs in which at least one twin has ALS have estimated ALS heritability to be around 76% (95% CI = 60–86%) when sporadic and familial cases are combined, and around 61% (95% CI = 38–78%) when only SALS cases are considered (Al-Chalabi et al., 2010). These findings suggest a major genetic role in both familial and sporadic ALS.

Genetic methodologies used to identify ALS genes

Linkage analysis

Many ALS pedigrees show classic Mendelian patterns of inheritance suggestive of highly penetrant mutations. FALS is mainly inherited in an autosomal dominant manner but autosomal recessive and X-linked inheritance have been reported (Deng et al., 2011; Gros-Louis et al., 2006; Hadano et al., 2001). Genetic traits showing Mendelian inheritance can be studied by linkage analysis which involves the calculation of the overall likelihood that a specific condition segregating in a specific pedigree is linked to a particular genetic marker, which is represented by the lod score (the logarithm of the odds of linkage) between the marker and the disease. Per definition, linkage is the tendency that genetic markers (here marker locus and disease locus) are inherited together as a consequence of their physical proximity on a single chromosome. The genetic basis of ALS remained an enigma until 1989 when the first locus (ALS1) associated with dominant familial adult-onset ALS was identified by linkage analysis to be on chromosome 21 (Siddique et al., 1989, 1991). The mutated gene in this locus was subsequently identified by single-strand conformational polymorphism analysis to be *SOD1* and direct sequencing of *SOD1* exons allowed the identification of several missense mutations (Rosen et al., 1993). To date, over 170 mutations have been reported in *SOD1* (see ALSoD (Abel et al., 2012), ALS online genetics database, http://alsod.iop.kcl.ac.uk/) and these account for approximately 20% of FALS cases. Following this success, classical linkage studies have led to the discovery of 10 new loci for ALS

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