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Review Article

Genomic and transcriptomic advances in amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder and the most common motor neuron disease. ALS shows substantial clinical and molecular heterogeneity. In vitro and in vivo models coupled with multiomic techniques have provided important contributions to unraveling the pathomechanisms underlying ALS. To date, despite promising results and accumulating knowledge, an effective treatment is still lacking. Here, we provide an overview of the literature on the use of genomics, epigenomics, transcriptomics and microRNAs to deeply investigate the molecular mechanisms developing and sustaining ALS. We report the most relevant genes implicated in ALS pathogenesis, discussing the use of different high-throughput sequencing techniques and the role of epigenomic modifications. Furthermore, we present transcriptomic studies discussing the most recent advances, from microarrays to bulk and single-cell RNA sequencing. Finally, we discuss the use of microRNAs as potential biomarkers and promising tools for molecular intervention. The integration of data from multiple omic approaches may provide new insights into pathogenic pathways in ALS by shedding light on diagnostic and prognostic biomarkers, helping to stratify patients into clinically relevant subgroups, revealing novel therapeutic targets and supporting the development of new effective therapies.

1. Introduction

Motor neuron diseases (MNDs) are a heterogeneous group of neurodegenerative disorders characterized by progressive loss of upper and lower motor neurons (MNs). Amyotrophic lateral sclerosis (ALS) is the most common MND, and affected patients may present with different clinical phenotypes associated with variable disease progression and prognosis. The broad molecular background and pathophysiological heterogeneity of ALS may contribute to the variety of clinical phenotypes. The pathological mechanisms underlying the disease include oxidative stress, inflammation, mitochondrial dysfunction, nucleocytoplasmic transport impairment, axonal transport defects and alterations in RNA processing (Goutman et al., 2022).

The analysis of clinical data and biological samples using a high-throughput approach may allow a more precise stratification of disease subtypes beyond improving both biomarker discovery and personalized treatment development. Multiomic approaches can quantify and integrate enormous amounts of data obtained from large samples in a forward-looking perspective toward the identification of new potential molecular pathways associated with the disease. Specifically, multiomic studies may be performed on human biological samples or on in vitro and in vivo ALS models.

In the Answer ALS (AALS) program, demographic and clinical data from ALS patients and multiomic data from patient-derived induced pluripotent stem cells (iPSCs) and MNs are being collected with the aim of building an open source of integrated clinical and biological records on ALS (Baxi et al., 2022). This program represents a robust and high-powered tool to extract and analyze data from biologically relevant

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subgroups to better understand pathogenic mechanisms, identify molecular targets and provide new potential biomarkers useful for therapeutic development. Given the wide phenotypic heterogeneity of ALS, a single biomarker is unlikely to encompass different disease subgroups or differentiate between patients and control subjects. Establishing panels of altered candidate and disease-relevant biomarkers by using multiomic approaches would facilitate the identification of specific signatures within a clinically heterogeneous population and help in the pursuit of personalized treatment.

In this review, we summarize the major findings obtained from genomic, epigenomic and transcriptomic studies on both patients and preclinical ALS models.

2. Genomics

ALS is a complex disease resulting from the interplay between background genetic susceptibility and time-locked exposure to environmental factors. According to the gene—environment-time theory (Bradley et al., 2018), ALS syndrome occurs after an external factor interacts, with a specific timing and duration of exposure, with a predisposing genetic setting. Heritability contribution in ALS has been estimated to reach a rate of 38–78% and 53% in twin studies and population registers, respectively (Al-Chalabi et al., 2010; Ryan et al., 2019).

ALS is mainly sporadic (sALS), but up to 10% of cases present familial recurrence (fALS). To date, more than 40 genes have been associated with both the sporadic and familial forms of the disease (Table 1).

Linkage and sequence analyses were instrumental in identifying the first causative gene of ALS in 1993, the copper-zinc superoxide dismutase 1 (*SOD1*) gene (Rosen et al., 1993; Siddique et al., 1991), of which more than 185 disease-related mutations have been reported thus far (Andersen and Al-Chalabi, 2011). Fifteen years after the discovery of *SOD1*, TAR DNA binding protein (*TARDBP*) and fused in sarcoma/-translocated in liposarcoma (*FUS*) were identified by linkage as causative genes for ALS (Kwiatkowski et al., 2009; Sreedharan et al., 2008). Both the *TARDBP* and *FUS* genes encode RNA binding proteins (RBPs) involved in several biological processes, such as transcription, RNA splicing, microRNA (miRNA) processing and mRNA transport. Disease-relevant *TARDBP* mutations include more than 50 missense variants that are mainly localized in the C-terminal region of exon 6, which is involved in protein—protein interactions (Chiò et al., 2011). Similarly, *FUS/TLS* mutations are mainly localized on exons 14 and 15 and often involve the C-terminal region, resulting in nuclear transport defects and subsequent FUS cytoplasmic mislocalization. Inheritance is typically autosomal dominant (AD) for both genes, although rare cases with an autosomal recessive (AR) pattern exist (Kwiatkowski et al., 2009). In 2011, through the use of genome-wide association studies (GWASs), two groups independently recognized a pathogenic hexanucleotide repeat expansion (HRE) in the chromosome 9 open reading frame 72 (*C9orf72)* on chromosome 9 as the most common genetic cause of ALS in the Caucasian population (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Pathogenic mechanisms underlying *C9orf72*-related ALS have been extensively reported elsewhere (Gagliardi et al., 2020).

Mutations in *C9orf72, SOD1, TARDBP* and *FUS* account for approximately 50% of fALS and 10% of sALS cases and are highly penetrant among individuals. However, mendelian forms of fALS represent only 10–15% of all cases. The remaining forms are usually associated with rare and/or low-penetrance variants, which modulate the disease risk and clinical phenotypes (Goutman et al., 2022). Some of these variants are extremely rare and are identified in single families (so-called private mutations). Other mutations, despite being relatively common, are not highly pathogenic, conferring an increased risk of developing ALS when occurring in combination with environmental factor exposure. Moreover, several studies have shown that the number of ALS patients and families carrying more than one pathogenic mutation in ALS causative genes is higher than expected (van Blitterswijk et al., 2012; Veldink, 2017; Zou et al., 2017) and might account for 1–4% of ALS patients (Cady et al., 2015; Dekker et al., 2016; Kenna et al., 2013; Morgan et al., 2017). These observations have led to the notion of oligogenic heritability in ALS, suggesting that more than one gene mutation would be needed for the disease phenotype to be fully expressed (Nguyen et al., 2018). Additional mutations may act as genetic modifiers of the disease phenotype, leading, for instance, to the development of frontotemporal dementia (FTD) or a combination of both ALS and FTD, or may influence the age of onset (Cady et al., 2015) or the severity of the disease (Pang et al., 2017). For all these reasons, large genomic studies on chip arrays might not always accurately identify extremely rare mutations or low-penetrance variants with a small pathogenic effect.

In this context, high-throughput DNA sequencing might be the most effective approach to explain much of the genetic landscape of ALS. Toward this goal, in Project MinE, samples from ALS patients and healthy individuals worldwide are currently being collected to map and compare the genetic profiles of 15000 ALS patients and 7500 controls (van der Spek et al., 2019).

2.1. Genome-wide association studies and susceptibility loci

The use of large-scale high-density GWAS arrays has enabled the discovery of some ALS causative genes. Specifically, GWASs aim to detect the association between genotype frequency and trait status. By exploring the additive genetic variance captured by common single-nucleotide polymorphisms (SNPs), GWASs have demonstrated the ability to identify possible common risk variants in large populations (McCarthy et al., 2008). Notably, the application of these approaches has led to the identification of *C9orf72* as the most common genetic cause of ALS in the Caucasian population. From this discovery, GWASs have further expanded the knowledge on ALS-associated genes.

Since 2007, several GWASs have been conducted with the aim of identifying genetic risk factors in sALS patients (Chiò et al., 2009; Cronin et al., 2008; Dunckley et al., 2007; Landers et al., 2009; Schymick et al., 2007; van Es et al., 2008, 2007). Variants in *FGGY* in the 1p32.1 region (Dunckley et al., 2007), *ITPR2* in the 12p11 region (van Es et al., 2007) and *DPP6* in the 7q36.2 region (Cronin et al., 2008; van Es et al., 2008) have been proposed as putative susceptibility genes for ALS. Nevertheless, these results have not been replicated in other GWASs, and the association between these *loci* and the disease has not been further confirmed (van Es et al., 2009). Indeed, since they include a relatively small number of patients, GWASs in ALS may have limited diagnostic power, leading to potentially misleading results.

The use of a two-step GWA approach (discovery and validation cohort) on approximately 20,000 individuals has enabled the identification of a variant in the intronic region of *UNC13A* (chromosome 19p13.11) and clarified the role of this region as a susceptibility region for ALS (van Es et al., 2009). In addition, the minor allele of rs12608932 in this locus has also been associated with reduced survival (Chiò et al., 2013; Diekstra et al., 2012). Proteins of the UNC13 group have a presynaptic localization and support synaptic transmission both in the peripheral nervous system (PNS) and central nervous system (CNS). TDP-43 inhibits cryptic exon-splicing events in *UNC13A,* and its dysregulation in ALS leads to the integration of a cryptic exon in *UNC13A* mRNA and to a decrease in levels of the UNC13A protein (Ma et al., 2022).

Joint analysis of data from comparable association studies can increase the detection of potential susceptibility genes. A large meta-analysis of 3959 Italian individuals and 11,611 US and European individuals from previously published studies screening almost 7 million SNPs led to the identification of a novel *locus* for sALS risk at 17q11.2 (Fogh et al., 2014). *SARM1*, the gene associated with this *locus*, is involved in Wallerian degeneration, but its role in ALS genetic susceptibility has not been further confirmed. Two *loci* at 1q32 and 22p11 were identified as susceptible regions for ALS in the Han Chinese population

Table 1
Genes associated with ALS.

Gene	Locus	Inheritance	Identification/level of evidence	Gene Disease Validity classification	fALS (%)	sALS (%)	Role in disease pathogenesis
ALS2	2q33.1	AR	Linkage analysis	Not established	< 1%	< 1%	Vesicular trafficking defects
ANG	14q11.2	AD; Risk factor	Candidate gene	Limited	< 1%	< 1%	Angiogenesis; stress granules formation
ANXA11	10q22.3	AD	WES	Definitive	~1%	~1,7%	Annexin A11 inclusions; defective binding to calcyclin; putative liquid-to-liquid phase separation (LLPS); vesicle trafficking
ATXN2	12q24.12	AD; risk factor	Candidate gene	Not established	< 1%	< 1%	Ribostasis defects; putative LLPS
C9orf72	9p21.2	AD	Linkage	Definitive	40%	7%	Altered RNA metabolism, proteostasis or autophagy; Impaired endosome trafficking and nucleocytoplasmic transport; LLPS; inflammation; DNA repair
C21orf2	21q22.3	Risk factor	WGS, GWAS	Not established	< 1%	< 1%	Cytoskeletal defects; DNA repair
CCNF	16p13.3	AD	Genome-wide linkage analysis, WES	Limited	~1–3,3%	< 1%	Cell-cycle regulation; Proteostasis defects
CHCHD10	22q11.23	AD	Linkage analysis	Not established	< 1%	< 1%	Role in mitochondrial cristae morphology maintenance and oxidative phosphorylation
CHMP2B	3p11.2	AD	Candidate gene	Definitive	< 1%	< 1%	Impaired proteostasis; vesicular trafficking defects
DCTN1	2p13.1	AD; risk factor	Linkage analysis	Not established	< 1%	< 1%	Axon trafficking defects
DNAJC7	17q21.2	Unknown	WES	Not established	< 1%	< 1%	Heat shock protein co-chaperone
DPP6	7q36.2	Unknown	GWAS - not confirmed in replication cohort	Not established	< 1%	< 1%	Dipeptidyl-peptidase-like protein; neuropeptides biological activity; expression and biophysical properties of voltage-gated potassium channels
ELP3	8p21.1	Unknown	Microsatellite association	Not established	< 1%	< 1%	Ribostasis defects; cytoskeletal defects
FGGY	1p32.1	Unknown	GWAS - not confirmed in replication cohort	Not established	< 1%	< 1%	Metabolite repair mechanism
FUS	16p11.2	AD; AR	Linkage analysis	Definitive	4%	1%	Ribostasis defects; nucleocytoplasmic transport defects; LLPS; DNA repair
GLT8D1	3p21.1	AD; risk factor	Linkage analysis	Not established	< 1%	< 1%	Glycosyltransferase
HNRNPA1	12q13.13	AD/de novo; risk factor	Linkage analysis	Not established	< 1%	< 1%	Ribostasis defects; LLPS
HNRNPA2B1	7p15.2	AD; risk factor	Linkage analysis	Limited	< 1%	< 1%	Ribostasis defects; LLPS
ITPR2	12p11.23	Unknown	GWAS - not confirmed in replication cohort	Not established	< 1%	< 1%	Inositol triphosphate receptor-mediated signaling
KIF5A	12q13.3	AD	GWAS	Not established	~0,5–3%	< 1%	Cytoskeletal and trafficking defects
MATR3	5q31.2	AD	Linkage analysis	Moderate	< 1%	< 1%	Ribostasis defects
MOBP	3p22.1	Risk factor	WGS, GWAS	Not established	< 1%	< 1%	Actin and myosin binding activity; constituent of myelin sheath; nervous system development
NEFH	22q12.2	AD; risk factor	Candidate gene	Not established	< 1%	< 1%	Axon trafficking defects
NEK1	4q33	Unknown	Exome sequencing	Definitive	~1–2%	< 1%	Cell-cycle regulation; axonal maintenance; DNA damage repair; protein aggregation
NIPA1	15q11.2	Unknown	GWAS	Not established	< 1%	< 1%	Nervous system development and maintenance
OPTN	10p13	AD; AR	Homozygosity mapping	Not established	< 1%	< 1%	Autophagy; inflammation; vesicle trafficking
PFN1	17p13.2	AD	Exome sequencing	Definitive	< 1%	< 1%	Cytoskeletal and trafficking defects; impaired axon growth
SARM1	17q11.2	Unknown	GWAS	Not established	< 1%	< 1%	Axonal degeneration following injury; positive regulation of neuron death; NAD catabolic process
SCFD1	14q12	Risk factor	WGS, GWAS	Not established	< 1%	< 1%	Autophagy; protein transport; vesicle-mediated transport; response to toxic substance
SETX	9q34.13	AD	Linkage analysis	Not established	< 1%	< 1%	Ribostasis defects; DNA and RNA processing
SOD1	21q22.11	AD; AR	Linkage analysis	Definitive	12%	1–2%	Proteostasis defects; oxidative stress; prion-like transmission; inflammation
SPG11	15q21.1	AR	Linkage analysis	Not established	< 1%	< 1%	DNA repair
SQSTM1	5q35.3	AD	Candidate gene	Not established	~1%	< 1%	Autophagy; inflammation
TARDBP	1p36.22	AD	Linkage analysis	Definitive	4%	1%	Transcription regulation; Ribostasis, proteostasis, and nucleo-cytoplasmic transport defects; LLPS; prion-like transmission; inflammation
TBK1	12q14.2	AD	WES	Not established	~3%	< 1%	Autophagy; inflammation; cell-cycle
TIA1	2p13.3	AD	GWAS	Not established	~2,2%	< 1%	Impaired RNA metabolism; LLPS
TNIP1	5q33.1	Unknown	GWAS	Not established	< 1%	< 1%	Inflammation; cell-cycle
TUBA4A	2q35	AD	Exome sequencing	Moderate	< 1%	< 1%	Cytoskeletal and trafficking defects
UBQLN2	Xp11.21	X-linked, AD	Linkage analysis	Definitive	< 1%	< 1%	Proteostasis defects; LLPS
UNC13A	19p13.11	AD	GWAS	Not established	< 1%	< 1%	Regulation of neurotransmitter release
VAPB	20q13.32	AD	Linkage analysis	Definitive	< 1%	< 1%	Proteostasis defects
VCP	9p13.3	AD	Candidate gene	Definitive	1%	1%	Proteostasis defects; inflammation; DNA repair and replication; cell-cycle

Gene Disease Validity Classification assigns the strength of a gene-disease association to one of the following clinical validity classes/categories: Definitive, Strong, Moderate, Limited, No Reported Evidence, or Conflicting Evidence Reported (McGlaughon et al., 2018) (ClinGen https://clinicalgenome.org/).

through a GWA approach (Deng et al., 2013). However, these loci were not found in a meta-analysis of GWA data collected from European individuals, suggesting the presence of high genetic heterogeneity across different ethnicities.

In 2018, a large-scale GWAS was performed on 12,663 ALS patients and 53,439 control subjects, including data from a previous meta-analysis (Nicolas et al., 2018). In addition to validating five previously identified *loci* (including *TNIP1*, *C9orf72*, *TBK1*, *UNC13A*, and *C21orf2)*, a strong correlation signal for five SNPs in linkage disequilibrium (LD) on chromosome 12q14.1 led to the identification of *KIF5A* as a disease-associated gene. *KIF5A* was identified in a previous study (Kenna et al., 2016) and in an earlier GWAS (van Rheenen et al., 2016) but failed to achieve genome-wide significance. KIF5A is a kinesin and encodes the neuronal heavy chain subunit of kinesin-1, which is involved in axonal transport. According to the findings of this study, the p.Pro986Leu variant may represent a relatively common risk allele for ALS, although its penetrance is moderately low. Conversely, loss of function (LOF) variants, identified by a rare variant burden analysis on exome sequencing data from more than 20,000 subjects, may represent rare but highly impactful risk factors. Interestingly, missense mutations in *KIF5A* have been associated with hereditary spastic paraplegia type 10 and Charcot-Marie-Tooth disease type 2. However, while these mutations are invariably in the N-terminal region, mutations responsible for ALS are mostly located in the C-terminal cargo binding region of the protein and mostly cause an LOF (Nicolas et al., 2018).

The most recent large-scale GWAS screened 29,612 ALS patients and 122,656 controls, identifying 15 risk *loci* for ALS. Combining data with previous whole-genome sequencing, the authors observed *NEK1* as the most robustly associated ALS risk gene. Furthermore, risk *loci* were shared across neurodegenerative diseases, with different enrichment patterns observed in different brain regions and cell types. Moreover, this work highlighted a role of impaired vesicular transport and autophagy in the pathogenesis of ALS, providing further evidence for cell autonomous disease initiation in glutamatergic neurons (van Rheenen et al., 2021).

Overall, large GWASs on seemingly sporadic ALS have allowed the identification of multiple common risk *loci* associated with the disease. However, most of these findings could not be replicated in independent populations, which would suggest that these *loci* harbor a small effect size on genetic susceptibility.

ALS heritability owing to common variants has been estimated to be 12%, which is lower than the heritability calculated with similar approaches for other late-onset neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Fogh et al., 2014). This finding may imply that ALS is a multifaceted condition with a greater contribution of low-frequency variants with high effect sizes, which are typically difficult to identify in conventional GWASs. In addition, rare variants conferring a high risk of developing the disease might be specific to individuals, families and ancestral populations, increasing the challenge of identifying genetic risk factors through GWASs.

2.2. Whole genome and whole exome sequencing

High-throughput DNA sequencing approaches have overcome the limitations of GWASs, enabling the discovery of highly pathogenic low-frequency variants. Whole genome sequencing (WGS) and whole exome sequencing (WES) are designed to capture rare variants, leading to invaluable advances in the identification of novel ALS-related genes such as *PFN1*, *TBK1, CHCHD10, TUBA4A, MATR3, CCNF, NEK1, C21orf2, ANXA11* and *TIA1* (Bannwarth et al., 2014; Cirulli et al., 2015; Freischmidt et al., 2015b; Johnson et al., 2014; Mackenzie et al., 2017; Smith et al., 2017; van Rheenen et al., 2016; Williams et al., 2016; Wu et al., 2012).

Exome sequencing of two large families with ALS has led to the identification of two different variants in the profilin 1 (*PFN1)* gene, located on chromosome 17 (Wu et al., 2012). Four additional mutations in the same gene have been recognized and confirmed in a cohort of 272 fALS patients. PFN1 is involved in the regulation of actin growth and polymerization. Mutant *PFN1*-expressing cells, but not wild-type cells, were found to display ubiquitinated aggregates, most of which expressed TDP-43, and showed impaired axonal outgrowth and reduced polymerized actin levels. These findings, along with functional studies on primary motor neurons, have suggested a causative role for *PFN1* in the ALS genetic architecture.

In 2015, a large-scale WES study on ALS patients together with a rare variant burden analysis identified TANK binding kinase 1 (*TBK1*) as a causative gene for ALS and FTD (Cirulli et al., 2015; Freischmidt et al., 2015b). *TBK1* encodes a multifunctional kinase associated with several cellular pathways, such as the immune response, autophagy and cell proliferation (Weidberg and Elazar, 2011). Most *TBK1* LOF variants cause a loss or reduction of kinase activity (Gijselinck et al., 2015). Conversely, missense mutations altering kinase activity or the substrate binding domain are considered risk alleles rather than causal variants (van der Zee et al., 2017). Linkage studies in multiple families coupled with replication studies in other cohorts as well as in vitro studies have confirmed that the pathogenic role of TBK1 is linked with autophagy and neuroinflammation.

Another WES analysis identified the missense mutation c .176 C>T; p.Ser59Leu in *CHCHD10* (Bannwarth et al., 2014), a gene encoding a mitochondrial protein (Genin et al., 2016). The first association with ALS was demonstrated in a family with a complex phenotype of ALS, FTD, cerebellar ataxia and mitochondrial myopathy (Bannwarth et al., 2014). Functional studies on patient fibroblasts and HeLa cells have validated the pathogenicity of this variant in ALS and have strengthened the role of mitochondrial dysfunction in ALS (Bannwarth et al., 2014).

Exome-wide rare variant burden analysis has detected several *TUBA4A* variants in ALS individuals (Smith et al., 2014). *TUBA4A* encodes tubulin alpha 4, a component of the cytoskeleton, and its variants have been correlated with a disruption of microtubule polymerization in vitro. Although *TUBA4A* mutations have been identified in pure FTD patients, variants in this gene are extremely rare in ALS cohorts, and there is still no evidence of cosegregation with the disease in affected families (Dols-Icardo et al., 2016; Li et al., 2018; Pensato et al., 2015; Perrone et al., 2017). Thus, evidence is still insufficient to support the role of *TUBA4A* mutations in ALS.

Another putative ALS-associated gene is *MATR3*, which is involved in the stabilization of certain mRNAs. In addition, this protein is able to interact with FUS and TDP-43; thus, mutations in this gene may cause nuclear export defects of TDP-43 and FUS mRNAs (Boehringer et al., 2017). *MATR3* mutations have been associated with ALS, as highlighted by exome sequencing in a Caucasian family including many subjects affected by ALS and dementia (Johnson et al., 2014). Exome sequencing has identified new additional variants in multiple families with ALS. *MATR3* overexpression in vivo has been shown to lead to hindlimb paralysis and forelimb muscle atrophy, suggesting a role in neuromuscular regulation (Moloney et al., 2018). Interestingly, MATR3 pathology has been observed in the spinal cord of ALS patients regardless of *MATR3* mutations (Johnson et al., 2014).

In 2016, *CCNF* was associated with ALS after the identification of a missense mutation in a large family with ALS/FTD and subsequent description of 20 other missense mutations (Williams et al., 2016). *CCNF* encodes cyclin F, which regulates genome stability through ubiquitin-mediated proteolysis. *CCNF* mutations impair the protein degradation system, leading to the accumulation of ubiquitinated proteins, including TDP-43 (Lee et al., 2018). Based on functional studies in *CCNF*-mutated zebrafish presenting disrupted axonal growth, ALS patients with *CCNF* mutations seem to present a toxic gain-of-function mechanism (Hogan et al., 2017).

A large WES analysis performed on 1022 fALS index cases identified LOF variants in *NEK1* (Kenna et al., 2016). The NEK1 protein is involved in cell cycle control, ciliogenesis, and mitochondrial membrane

regulation and participates in cytoskeletal dynamics in neurons (Kenna et al., 2016). In parallel, van Rheenen and colleagues described a new risk locus on chromosome 21 and identified *C21orf2* as an ALS-associated gene (van Rheenen et al., 2016). In this study, they employed high-coverage WGS data from 1246 ALS patients and 615 controls as a reference panel and analyzed the genotyped data from a very large number of individuals (12,577 cases and 23,475 controls). Notably, both NEK1 and C21orf2 are involved in DNA damage repair, and their recessive mutations are associated with axial spondylometaphyseal dysplasia (Fang et al., 2015). However, data confirming the cosegregation of *NEK1* and *C21orf2* with fALS are still lacking, and replication data in ALS cohorts are limited; thus, the contribution of *NEK1* and *C21orf2* to ALS remains to be determined.

Missense mutations in *ANXA11* have been identified in 751 fALS patients by exome sequencing and are associated with typical ALS-related p62 and TDP-43 pathology in postmortem tissues (Smith et al., 2017). The encoded protein plays a role in vesicle trafficking, apoptosis, and exocytosis. The presence of the *ANXA11* founder mutation in affected relatives from different families and other mutations in unrelated individuals supports its function as a genetic determinant in ALS. Pathological aggregation of ANXA11 causes the sequestration of the wild-type protein and increases its propensity to aggregate (Smith et al., 2017).

Finally, exome sequencing analysis performed in a European family with ALS/FTD with TDP-43 brain pathology identified a missense mutation in the *TIA1* gene (Mackenzie et al., 2017). *TIA1* encodes an RBP containing prion-like low complexity domain (LCD) that can assemble into membrane-less organelles, such as stress granules (SGs). Genetic screening of 1039 ALS/FTD individuals has led to the discovery of additional nonsynonymous variants in LCD domains of *TIA1*. Mutated *TIA1* is associated with alterations in SG dynamics and TDP-43 aggregation. However, given the lack of confirmed cosegregation data in families with ALS, the genetic role of *TIA1* in ALS/FTD needs to be further elucidated. In this regard, the Project Mine Consortium has re-examined the findings by Mackenzie and colleagues and performed a burden analysis of TIA1 exon 11–13 in the Project Mine dataset, without yielding any significant results underpinning its causal role in ALS (van der Spek et al., 2019).

Overall, the lack of insufficient genetic evidence supporting the causality of certain mutations has caused some previously described genetic associations to be subsequently disproved.

2.3. Short tandem repeats

Short tandem repeats (STRs) are short DNA sequences (between 2 and 12 base pairs) that constitute approximately 3% of the human genome. STRs are intrinsically unstable, and their variation in repeat length largely contributes to gene regulation (Malik et al., 2021). However, repeat instability and expansion beyond a pathogenic threshold in certain genes induce architectural changes in DNA and toxicity from both gain- and loss-of-function mechanisms, which ultimately result in disorders mainly affecting the CNS.

The identification of HRE in *C9orf72* as the most common genetic cause of ALS has supported the role of STRs in the genetic background of ALS. Additionally, other disease-associated repeats have been identified as genetic risk factors.

The technological advances of recent years have dramatically improved the identification of STRs and have made possible the detection of repeat expansions through next-generation sequencing (NGS) approaches (Coutelier et al., 2022). However, the low detection rate and the failure to determine the exact breakpoints (typically occurring in highly repetitive regions of the genome that are poorly covered by short-read WGS) still represent important limitations.

The introduction of third-generation sequencing approaches that have improved the mapping of repetitive regions (long-read sequencing) and the combination of WGS with bioinformatic and computational tools have considerably improved the characterization of structural variants and STRs and their transcriptional effects, paving the way for a deeper understanding of the genomic basis of complex diseases (Chintalaphani et al., 2021).

Intermediate-length repeat expansions in *ATXN2,* which are the cause of spinocerebellar ataxia 2 (SCA2) when present in larger sizes, have been associated with an increased risk of sALS (Elden et al., 2010). Indeed, the co-occurrence of *C9orf72* and *ATXN2* expansions in sALS patients is relatively common (Lattante et al., 2014), suggesting that *ATXN2* might act as a disease modifier of *C9orf72*. Moreover, in vitro and in vivo studies have highlighted ATXN2 interactions with TDP-43 and have shown that antisense oligonucleotide (ASO) mediated silencing of *ATXN2* improved survival and reduced TDP-43 pathology in ALS mouse models (Becker et al., 2017; Elden et al., 2010).

Although a large copy number variation (CNV) association study exploring the role of rare CNVs in ALS susceptibility was inconsistent in finding differences between patients and controls (Blauw et al., 2010), the polyglutamine expansion in *NIPA1* has been suggested to be associated with ALS. These results have been confirmed in another independent replication study (Tazelaar et al., 2019).

Moreover, the co-occurrence of ALS and SCA1 in two unrelated pedigrees and the finding of intermediate CAG repeats in *ATXN1* in a patient with ALS (Spataro and La Bella, 2014; Tazelaar et al., 2020) have raised suspicion for a genetic link between *ATXN1* repeats and ALS. In a large-scale genetic association study involving 11,700 individuals, a significant correlation between intermediate-length *ATXN1* repeat expansions and ALS was revealed and further corroborated by functional experiments in Drosophila models (Tazelaar et al., 2020).

Similarly, pathogenic expansions in the range of 40–64 repeats in the huntingtin (*HTT*) gene have been detected by WGS analysis in 3 out of 2442 patients with ALS/FTD and not in controls or Lewy-body dementia (LBD)-affected patients (Dewan et al., 2021). These findings have been replicated in an independent cohort, and a novel case of ALS with HTT expansion has also been reported by our group (Manini et al., 2022). In vitro studies have shown that CAG repeats in *HTT* can induce TDP-43 and Huntingtin coaggregation, likely through a direct interaction between polyglutamine (poly-Q) residues and the TDP-43 C-terminal domain (Coudert et al., 2019). These findings suggest the importance of CAG repeats in ALS pathomechanisms, but a pathogenic role of *HTT* expansions in ALS has not yet been demonstrated.

In a recent study of a Chinese population, GGC repeat expansion in *NOTCH2NLC* was observed in 4 out of 545 patients with ALS and was postulated to modulate the disease phenotype, characterized by aggressive disease and rapid deterioration (Yuan et al., 2020). Replication studies in several cohorts of ALS patients failed to detect *NOTCH2NLC* expansions (Jih et al., 2021; Manini et al., 2023).

3. Epigenomics

Epigenetics refers to the genome-independent heritable modifications of the genome derived from the interaction between environmental and individual genetic factors. DNA methylation, histone remodeling, RNA editing and miRNAs represent the main epigenetic determinants involved in neural development, plasticity and aging (Qureshi and Mehler, 2013; Staszewski and Prinz, 2014) playing a putative role in ALS progression (Bennett et al., 2019; Figueroa-Romero et al., 2012). The reversibility of epigenetic changes supports their potential role as versatile therapeutic targets in ALS (Paez-Colasante et al., 2015).

3.1. DNA methylation

DNA methylation involves the posttranscriptional covalent addition of a methyl group to cytosine residues in DNA by DNA-(cytosine-5)-methyltransferase (DNMT) enzymes, which leads to 5-methylcytosine (5mC) modification (Chestnut et al., 2011). Chromatin structure

alterations occur as a consequence of 5mC formation (Choy et al., 2010). CpG dinucleotides within promoter elements represent preferential sites of DNA methylation, as well as other regions implied in genomic regulation (Qureshi and Mehler, 2013). 5mCs exert opposite effects depending on their localization in intragenic or promoter regions. Accordingly, 5mCs located in promoter regions negatively regulate gene expression despite the inhibition of chromatin-remodeling proteins, whereas their intragenic localization promotes gene expression (Qureshi and Mehler, 2013).

Reversible DNA methylation mechanisms may be involved in disease pathogenesis. *DNMT3A* encodes DNMT, which is overexpressed in the CNS of ALS patients. An increase in DNMT levels was associated with in vitro cell death in MN-like cells (Chestnut et al., 2011). Similarly, enhanced global DNA 5mC and 5hmC were also present in blood and neural samples from ALS patients (Chestnut et al., 2011; Figueroa-Romero et al., 2012; Tremolizzo et al., 2014). Other findings include the *OPTN* hypomethylated state, as shown in genome-wide methylation array studies (Figueroa-Romero et al., 2012), and a loss of function of *PRMT1* causing histone code changes as a consequence of altered FUS cellular redistribution (Tibshirani et al., 2015).

A hypermethylation of CpG islands in the *C9orf72* HRE has also been described in various *C9orf72*-related ALS studies (Xi et al., 2013). *C9orf72* promoter methylation might have a protective role against the abnormalities present in the HRE. Transcriptional silencing of *C9orf72* occurred in patient-derived lymphoblast cell lines as a result of promoter hypermethylation, whereas demethylation reversed these protective processes (Liu et al., 2014). Methylation levels were indeed significantly higher in blood collected from frontotemporal lobar degeneration (FTLD) patients harboring the HRE in *C9orf72* than in noncarriers (Belzil et al., 2014; Xi et al., 2014). Altogether, these results support the evidence that altered DNA methylation could play a critical role underlying neurodegeneration in ALS pathogenesis.

ALS risk factors and disease progression can be related to DNA methylation patterns. A large epigenome-wide association study performed on ALS and healthy blood samples identified multiple differentially methylated positions in several genes associated with metabolism, cholesterol biosynthesis, and immunity (Hop et al., 2022). These findings, together with the data derived from a more recent GWAS, have shown that cholesterol biosynthesis is potentially linked to ALS. Finally, DNA methylation levels were correlated with patient survival rates, suggesting that they could act as predictors of underlying disease processes potentially sensitive to therapeutic treatments (Hop et al., 2022).

Recent studies have evaluated epigenetic modifications of mitochondrial DNA (mtDNA) in ALS (Jimenez-Pacheco et al., 2017; Stoccoro et al., 2018). For instance, *DNMT3A* was upregulated in postmortem mitochondrial fractions of the ALS motor cortex (Wong et al., 2013). Neuronal mitochondria from individuals with *SOD1* and *C9orf72* mutations presented variations in 5mC and *DNMT1* (Chestnut et al., 2011) associated with a global increase in mtDNA copy number. Moreover, *SOD1* carriers exhibited reduced methylation in the D-loop region, a possible compensatory mechanism for the overall upregulation of mtDNA (Stoccoro et al., 2018).

This evidence may suggest a role of mtDNA epigenetic modulation in ALS pathogenesis as well as in determining susceptibility to environmental stimuli (Iacobazzi et al., 2013).

3.2. Histone modifications

Histone acetylation is a posttranslational modification of nucleosomes mediated by histone acetyltransferases (HATs). Histone acetylation alters the accessibility of DNA to transcription factors (Feng et al., 2015) by loosening chromatin, thereby enabling transcriptional activation. Histone deacetylation catalyzed by histone deacetylases (HDACs) exerts the opposite effect (Feng et al., 2015; Probst et al., 2009). Indeed, the dynamic equilibrium of histone acetylation and deacetylation acts as a major regulator of gene expression in eukaryotes (Park and Kim, 2020).

Different models of neurodegenerative diseases, including ALS, present a global reduction in histone acetylation with an imbalance between HATs and HDACs (Lagali and Picketts, 2012; Naia et al., 2017; Rouaux et al., 2003). Among the eighteen human HDACs, several isoforms have been linked to ALS pathomechanisms (Bardai et al., 2012; Broide et al., 2007; Bruneteau et al., 2013; Buonvicino et al., 2018; Chen et al., 2015; Cohen et al., 2015; Gal et al., 2013; Janssen et al., 2010; Kim et al., 2010; Li et al., 2019; Pigna et al., 2019; Riva et al., 2016; Sanna et al., 2020; Taes et al., 2013; Valle et al., 2014). The first HDAC isoform (HDAC1) is primarily found in the nucleus of neurons, astrocytes and oligodendrocytes (Jia et al., 2012), where it exerts a transcriptional repression function (Broide et al., 2007). Depending on cellular localization, HDAC1 is reported to have both neuroprotective and neurotoxic effects. Conventionally localized in the nucleus, within the cytoplasm, HDAC1 impairs the formation of cargo proteins by binding motor proteins and α-tubulin, leading to a disruption of axonal transport. HDAC1 represents a TDP-43 interacting protein, and its inhibition resulted in a protective effect against TDP-43 toxicity, as demonstrated in both in vivo and in vitro models (Sanna et al., 2020). Other relevant findings include impaired nuclear localization of p53 and HDAC1 following ER stress in the $SOD1^{G93A}$ mouse model (Li et al., 2019).

HDAC1 exhibits its neurotoxic effect when interacting with protein isoform 3 (HDAC3), which selectively induces neuronal death. Indeed, the two proteins share structural similarity, and their interaction is strongly increased during neurodegeneration both in vitro and in vivo (Bardai et al., 2012). Notably, HDAC3 has been implicated in ALS neurodegeneration, mostly through the promotion of transcriptional repression (Bardai and D'Mello, 2011; Broide et al., 2007). HDAC isoform 2 (HDAC2) exhibits structural similarity with HDAC1 and HDAC3 and is part of the same HDAC class (Park and Kim, 2020). HDAC2 plays a role in regulating gene expression and coordinating neuronal differentiation and axonal regeneration and is potentially neurotoxic in ALS (Broide et al., 2007). Some findings suggest that HDAC2 may be overexpressed in the motor cortex and spinal cord of ALS patients (Janssen et al., 2010) and potentially implicated in glutamate metabolism (Riva et al., 2016).

HDAC class II includes HDAC4, HDAC5, HDAC6 and other isoforms. HDAC4 is expressed in dendritic spines and may exert neuroprotective or neurotoxic effects depending on its cellular localization, similar to HDAC1. HDAC4 and its regulator miRNA-206 may drive collateral neuronal sprouting after motor neuron loss in ALS (Bruneteau et al., 2013; Echaniz-Laguna et al., 2008; Williams et al., 2009). Consistently, HDAC4 is overexpressed in $SOD1^{G93A}$ mice and ALS patients (Bruneteau et al., 2013; Buonvicino et al., 2018; Pigna et al., 2019). Interestingly, muscle biopsy samples from patients with rapidly progressing ALS showed increased HDAC4 transcription compared to those from patients with a slower progression rate. Hence, HDAC4 upregulation might exert negative feedback on muscle reinnervation (Bruneteau et al., 2013). Another study supported a neuroprotective role for HDAC4, highlighting that its depletion in the skeletal muscles of $SOD1^{G93A}$ mice was correlated with ALS symptoms, while its increase was associated with a more favorable phenotype. Moreover, the knockout of HDAC4 in skeletal muscles worsened pathological hallmarks in rodents, thus suggesting its role in promoting muscle denervation and atrophy (Pigna et al., 2019).

HDAC5 regulates DNA transcription in both peripheral tissue and the brain (Broide et al., 2007) by shuttling between the nucleus and the cytoplasm and playing a neuroprotective role (McKinsey et al., 2000). A decrease in HDAC5 transcript and protein levels was associated with disease progression in the spinal cord of both $SOD1^{G93A}$ and $SOD1^{G86R}$ murine models (Valle et al., 2014). Moreover, a reduction in HDAC5 protein levels was detected upon the expression of $SOD1^{G93A}$ in SH-SY5Y neuroblastoma cells (Valle et al., 2014).

Like most of the deacetylating enzymes described thus far, HDAC6 seems to have opposite effects on neuronal health. Indeed, conflicting results have been reported regarding the role of this enzyme in ALS.

Nevertheless, multiple studies support the importance of HDAC6 as a possible therapeutic target for neurodegeneration. HDAC6 is mostly restricted to the cytoplasm and is mainly recognized as a specific deacetylase of α-tubulin. However, HDAC6 has been described to act on many other substrates, such as tau and TDP-43 (Hubbert et al., 2002). Notably, TDP-43 acetylation may prompt TDP-43 accumulation. Since HDAC6 could drive TDP-43 deacetylation, impairing HDAC6 activity could trigger TDP-43 aggregation (Cohen et al., 2015).

HDAC6 transcripts were shown to be increased in $SOD1^{G93A}$ model mice, and its knockdown was found to be neuroprotective, with extended survival following the onset of disease (Taes et al., 2013). In contrast, in another in vivo study, HDAC6 overexpression obtained by intraventricular lentivirus injection in a $SOD1^{G93A}$ rodent model rescued the disease phenotype (Chen et al., 2015). Similarly, in vitro studies showed that the knockdown of HDAC6 can drive the accumulation of mutant SOD1 (Gal et al., 2013). TDP-43 and FUS knockdown reduced HDAC6 transcript levels (Kim et al., 2010). Last, Guo et al. reported that partial knockdown of HDAC6 mediated by ASOs was able to rescue the disrupted axonal transport observed in in vitro models of *FUS*-ALS (Guo et al., 2017).

4. Transcriptomics

Over the years, transcriptomic techniques have provided very important information on the molecular pathways involved in ALS, allowing the identification of specific biological markers that may be useful for diagnosis and prognosis (Pradat et al., 2012; Recabarren-Leiva and Alarcón, 2018; Saris et al., 2009).

Early results were obtained with microarrays and RNA sequencing, yielding remarkable insights. Technological advances in RNA sequencing have led to the development of sophisticated methods, such as single-cell RNA sequencing (scRNA-seq), that are able to identify the transcriptomic profile of individual cells.

Nevertheless, the molecular mechanisms underlying the disease remain almost unknown. RNA metabolism disruption is a well-recognized contributor to ALS pathogenesis (Butti and Patten, 2019; Wolozin and Ivanov, 2019). As a result of altered gene expression in ALS, RBP segregation occurs together with the impairment of SG dynamics, leading to disrupted mRNA stability and processing (Wolozin and Ivanov, 2019). Furthermore, transcriptomic analyses have highlighted, among ALS dysregulated molecular pathways, the importance of overall upregulation of neuroinflammation and cell death processes as well as the downregulation of neuronal-specific genes, providing clues for the development of new therapeutic strategies (D'Erchia et al., 2017). All differentially expressed genes (DEGs) identified in transcriptomic studies are listed in Table 2.

4.1. Microarrays

First transcriptomic analysis were carried out using microarray

Table 2
Differentially expressed genes (DEGs) in ALS.

Tissue	Genes	Up/Down regulation	Biological meaning	Identification method	References
SOD1 mice spinal cord	*Gfap, Itgam*	Up	Loss of neuronal cells and increased proliferation of microglia	Microarray	Yamashita et al. (2022)
	Mnx1	Down			
Microglia of SOD1 mice spinal cord	*Apoe*	Up	Clearance of extracellular aggregates of SOD1	Microarray	Yamashita et al. (2022)
	TREM				
	Cx3cr1, Ccl3, Ccl6, Ccl9, Cxcl16		Immunological response		
	Sparc, Clu, Fos		Pro-inflammatory phenotype	Single-cell RNA sequencing	MacLean et al. (2022)
Astrocytes of SOD1 mice spinal cord	*Abca1, Clu*	Up	Increase of lipoprotein secretion	Microarray	Yamashita et al. (2022)
	Cdh22	Down	Altered cell-cell communication	Single-cell RNA sequencing	MacLean et al. (2022)
	Cav2	Up			
	Pparg	Up	Putative re-myelination		
Oligodendrocytes of SOD1 mice spinal cord	*Plat, Klk6*	Up	Neurotoxicity	Microarray	Yamashita et al. (2022)
Neurons of SOD1 mice spinal cord	*Met, Sulf1, Igf1, HspB6, Hsp25*	Up	Immunoreactivity, neurotrophic and anti-apoptotic pathways	Microarray	Yamashita et al. (2022)
Motor neurons of SOD1 mice spinal cord	*Epha3*	Down	Neuroprotection	Single-cell RNA sequencing	MacLean et al. (2022)
Muscles of ALS patients	*CERKL*	Up	Protection against oxidative stress	Microarray	Shtilbans et al. (2011); Tuson et al. (2009)
	ANKRD1 GADD45α	Up	Injury response, cell death		Shtilbans et al. (2011); Gonzalez de Aguilar et al. (2008); Pradat et al. (2012)
	GPD1	Down	Muscle impairment, neurogenic atrophy		Jimi et al. (2004);
	AQP4				Pradat et al. (2012)
ALS post-mortem human tissues	*SNAP25, SNPH, STX1B, SYT4*	Down	Synaptic function	RNA sequencing	D'Erchia et al. (2017); Wang et al. (2021)
	CHAT, HTR2C, SLC1A2, SLC12A5		Impulse transmission		
	CACNA1G, GRIN1, GRIN2		Calcium metabolism		
ALS human CNS	*EGR1*	Up	Neuronal plasticity, tau hyperphosphorylation and microtubule destabilization	RNA sequencing	Recabarren-Leiva and Alarcón (2018)
	GABRA1	Down	Autophagy, excitotoxicity and TDP43 aggregate formation		
ALS patients' spinal cord	*PTPN23*	Up	Regulation of survival motor neuron (SMN) complex	RNA sequencing	Husedzinovic et al. (2015)
	KPNA3, TMED2	Up	DPR toxicity associated with *C9orf72* mutations		Jovičić et al. (2015)
	NCOA4	Up	Autophagic turnover of ferritin		Mancias et al. (2014); Quiles del Rey and Mancias (2019)

technology, exploiting the hybridization of fluorescently labeled cDNAs with a collection of microscopic DNA probes spotted on these devices, enabling the measurement of the expression level of multiple genes simultaneously (Clark et al., 2002). Indeed, microarrays have been widely used for transcriptional profiling due to the low cost of an efficient high-throughput analysis with a relatively easy technology (Cheng et al., 2005; Lowe et al., 2017; Schena et al., 1995). Together with classic microarrays, genomic tiling microarrays were developed to map large areas of the genome with high resolution to elucidate the transcribed regions of the entire human genome (Bertone et al., 2004).

Specifically for ALS, early microarray studies performed on postmortem CNS samples as well as on murine disease models have yielded invaluable data to deeply investigate the molecular changes and biological pathways associated with neurodegeneration (Dangond et al., 2004; Ferraiuolo et al., 2007; Ishigaki et al., 2002; Malaspina et al., 2001; Offen et al., 2009; Wang et al., 2006).

Several microarray studies have been performed on whole blood samples, lymphocytes and muscle samples of ALS patients, shedding light on how the pathology affects not only the transcriptome of the CNS but also the gene expression profile of peripheral tissues (Mougeot et al., 2011; Pradat et al., 2012; Shtilbans et al., 2011). Indeed, many relevant DEGs have been identified in muscle samples from ALS patients, including a significant upregulation of the genes leucine-rich repeat kinase 2 (*LRRK2)*, ceramide kinase-like (*CERKL)*, ankyrin repeat domain 1 (*ANKRD1)* and growth arrest and DNA damage inducible alpha (*GADD45α)* (Shtilbans et al., 2011). Interestingly, the upregulation of *CERKL* has been described as protective against oxidative stress, preventing cells from entering the apoptosis induced by oxidative stress conditions (Tuson et al., 2009). Furthermore, mutations in *LRRK2* are known to be associated with neurodegeneration since this gene has been widely investigated in Parkinson's disease (Dächsel and Farrer, 2010; Paisán-Ruiz et al., 2013; Rui et al., 2018). Finally, the upregulation of *ANKRD1* and *GADD45α* has also been observed in SOD1 mice (Gonzalez de Aguilar et al., 2008). *ANKRD1* and *GADD45α* dysregulation was confirmed in the skeletal muscles of patients at different stages of disease to assess alterations in gene expression levels that could reflect the degree of ALS severity (Pradat et al., 2012). An upregulation of myogenin (*MYOG)*, the acetylcholine receptor subunits *CHRNG* and *CHRNA1*, the zinc finger protein *ZFP36L2,* ankyrin repeat domain 10 (*ANKRD10*) and myosin binding protein H (*MYBPH*) was identified among DEGs. In addition, glycerol-3-phosphate dehydrogenase 1 (*GPD1*) and water-selective channel aquaporin 4 (*AQP4*) gene expression dysregulation was described, which correlated inversely with the disease progression rate (Jimi et al., 2004; Pradat et al., 2012).

Microarray studies performed in murine ALS models have identified multiple DEGs in the spinal cord of SOD1 mice (Yamashita et al., 2022), with a subset of 207 genes found to be dysregulated. Among DEGs, the authors described *Met*, *Sulf1* and *Igf1* as being particularly enriched in neurons together with other significant DEGs specific to MNs, such as *Casp12* and the two heat shock proteins *HspB6* and *Hsp25* (Yamashita et al., 2022). Notably, the decreased levels of the motor neuronal marker *Mnx1* and increased levels of *Gfap* and *Itgam* were in line with the loss of neuronal cells and increased proliferation or activation of microglia, which correlated well with disease pathogenesis (Yamashita et al., 2022). *Plat, Klk6* and multiple chemokine-associated genes, such as *Cx3cr1*, *Ccl3, Ccl6, Ccl9* and *Cxcl16,* were specifically enriched in oligodendrocytes and microglia, while apolipoprotein E (*Apoe)* was enriched both in astrocytes and microglia. The concurrent microglia-specific upregulation of *Apoe* and triggering receptor expressed on myeloid cells 2 (*Trem2)* supports the existence of a mechanism responsible for the clearance of extracellular aggregates of SOD1 in ALS (Yamashita et al., 2022). Indeed, the Trem2 receptor has already been described in the microglia of Alzheimer's disease conditions as being responsible for a similar mechanism associated with lipoprotein-Aβ complex uptake (Yeh et al., 2016). In addition, it has been demonstrated that TREM2-APOE can regulate the expression of proinflammatory miR-155 in SOD1-ALS mouse microglia (Butovsky et al., 2015, 2012; Krasemann et al., 2017). Within astrocytes, an upregulation of genes involved in lipid transport, such as *Abca1* and *Clu,* has also been observed, suggesting how the diseased phenotype might lead to increased lipoprotein secretion (Yamashita et al., 2022).

Overall, microarrays remain a very useful technique for transcriptomic profiling, and they are inexpensive and currently easy to perform from a bioinformatic point of view. However, microarrays have many limitations since only genes whose sequence is known can be evaluated. Furthermore, technical troubles related to cross-hybridization as well as hurdles related to the analysis of extremely poorly expressed genes are encountered in microarrays (Kukurba and Montgomery, 2015; Okoniewski and Miller, 2006; Royce et al., 2007; Wang et al., 2009). In recent years, the majority of transcriptomic studies have exploited next generation sequencing-based approaches (NGS), such as RNA sequencing (RNA-seq) and single-cell RNA sequencing (scRNA-seq), that overcome some of those constraints and offer the potential to extract information.

4.2. RNA sequencing

RNA sequencing allows quantitative expression analysis of the transcriptome to provide data on alternative splicing and transcript assembly for the discovery of new transcripts (Chu and Corey, 2012; Kukurba and Montgomery, 2015). Furthermore, RNA sequencing enables the analysis of pre-mRNA, total RNA and noncoding RNAs, such as lncRNAs, circRNAs and miRNAs (Kukurba and Montgomery, 2015). Hence, bulk RNA sequencing exploits the capabilities of high-throughput sequencing methods to provide an accurate measurement of the transcript levels of all cells within a biological sample, overcoming many of the limitations associated with microarray technology (Kukurba and Montgomery, 2015; Malone and Oliver, 2011; Reis-Filho, 2009).

RNA-sequencing studies revealed that mutations in *FUS* affect ribosome and spliceosome-related genes, inducing alternative splicing events (Lagier-Tourenne et al., 2012; van Blitterswijk et al., 2013). Furthermore, enrichment analysis of human and murine neurons derived from embryonic stem cells highlighted the role of FUS in controlling neuronal function, neurite outgrowth, axon formation, calcium homeostasis and mitochondrial functions (Nakaya et al., 2013).

In the same years, brain RNA sequencing of SOD1 ALS mice revealed how misfolded SOD1 protein is able to interact with other cytosolic or membrane proteins, modifying their role in cellular trafficking, synaptic function and organellar functionality (Bandyopadhyay et al., 2013).

Whole transcriptome sequencing of the spinal cord ventral horns of sALS patients led to the identification of 1160 DEGs. Among these genes, glial-derived genes and others linked with neuroinflammation or cell death showed a trend toward upregulation (D'Erchia et al., 2017). A dysregulation of the same pathways was confirmed by RNA sequencing analysis of the thoracic, lumbar and cervical spinal cord regions of ALS patients, which identified many genes coding for proteins secreted by activated macrophages and microglia, including *CCL18*, *CHIT1*, *CHRNA1*, *GPNMB* and *LYZ* (Humphrey et al., 2023).

An impairment in cell type abundance between cases and controls has been associated with a dysregulation of neuroinflammatory pathways in postmortem motor cortex samples, supporting the existence of a molecular signature associated with the disease inflammatory status (Morello et al., 2017a). Similarly, Dols-Icardo's group performed a massive transcriptomic analysis of ALS motor cortex samples and showed an enrichment of neuroinflammatory and synaptic-related pathways, providing further support for the role of microglial neuroinflammatory changes in ALS. Among 124 DEGs, the authors identified an upregulation of chitinase-related genes *CHI3L1* and *CHI3L2* (Dols-Icardo et al., 2020). Notably, several studies performed in cerebrospinal fluid (CSF) identified higher concentrations of chitinases in ALS patients, supporting their potential role as neuroinflammatory biomarkers (Gille

et al., 2019; Illán-Gala et al., 2018; Oeckl et al., 2020; Thompson et al., 2021, 2019, 2018; Vu et al., 2020).

In addition to neuroinflammation, ALS postmortem human tissues showed a global downregulation of neuronal-specific genes involved in different biological processes, such as synaptic function (*SNAP25, SNPH, STX1B, SYT4*), impulse transmission (*CHAT*, *HTR2C*, *SLC1A2*, *SLC12A5*) and calcium metabolism (*CACNA1G*, *GRIN1*, *GRIN2A*) (D'Erchia et al., 2017; Wang et al., 2021). Several other genes, including *AQP1*, *SLC14A1*, *MT1X*, *DSCR1L1*, *PCP4*, *UCHL1*, *GABRA1*, *EGR1*, *OLFM1* and *VSNL1,* exhibited altered expression patterns in the patient motor cortex and spinal cord, establishing their possible utility as novel markers associated with ALS risk. Specifically, *EGR1* is involved in neuronal plasticity and was upregulated in postmortem ALS CNS samples, promoting tau hyperphosphorylation and microtubule destabilization. Conversely, γ-aminobutyric acid A receptor 1 (*GABRA1*) levels were downregulated in ALS, with putative involvement in disease pathogenesis by enhancing autophagy, excitotoxicity and TDP-43 aggregate formation in affected neurons (Recabarren-Leiva and Alarcón, 2018).

In 2021, Wang's group described altered expression of several genes involved in RNA metabolism (PTPN23), nucleocytoplasmic transport (*KPNA3* and *TMED2*) and autophagy (*NCOA4*) in the spinal cord of ALS patients (Wang et al., 2021). In particular, *PTPN23* belongs to the family of nonreceptor-type tyrosine phosphatases, regulates the survival motor neuron (SMN) complex and mediates pre-mRNA processing in MNs (Husedzinovic et al., 2015). *KPNA3* and *TMED2* acted as modifiers of DPR toxicity in ALS cases associated with *C9orf72* mutations (Jovičić et al., 2015), while *NCOA4*, a selective cargo receptor for autophagic turnover of ferritin, was implicated in ferritinophagy in neurodegeneration (Mancias et al., 2014; Quiles del Rey and Mancias, 2019).

Taken together, RNA-seq is a powerful tool to identify molecular changes in patient biological samples that can be used to elucidate local processes and identify potential therapeutic targets.

4.3. Single-cell RNA sequencing

In the last decade, scRNA-seq approaches have become the mainstay of transcriptomic analysis (Hashimshony et al., 2012; Islam et al., 2014, 2011; Ramsköld et al., 2012; Tang et al., 2009; Zeisel et al., 2015). The great advantage of scRNA-seq lies in the possibility of concurrently sequencing thousands of cells and investigating single-cell expression profiles as well as transcriptomic alterations in diseases (Islam et al., 2014; Liu et al., 2020). Compared to bulk RNA-sequencing, which allows the investigation of the average transcriptomic profile of a mixture of cells within a biological sample, scRNA-seq enables the ascertainment of the cell-by-cell expression level, thus overcoming the issue of heterogeneity within cell populations and yielding more biological insights than traditional RNA-sequencing technologies (Yip et al., 2019). Although scRNA-seq has become one of the most promising transcriptomic approaches, several aspects need to be considered when using this method since the transcriptome could change in response to sample manipulation. As a matter of fact, the classic single-cell approach needs PCR-based amplification, which could lead to errors and alter the relative abundance of the different mRNAs throughout the process. Furthermore, the sensitivity of the method could be an issue for genes with low expression (Eberwine et al., 2014; Islam et al., 2014). By exploiting the potential of scRNA-seq, Liu and colleagues investigated DEGs within the pontine brainstem of symptomatic SOD1 mice and controls to deeply investigate the involvement of different cell populations in the pathophysiological mechanisms underlying the disease (Liu et al., 2020). Indeed, most of the cell types showed transcriptomic alterations, proving that the disease affects not only MNs but also astrocytes, neurons, oligodendrocytes, microglia, ependymal cells and Schwann cells. Cell type-specific alterations in synaptic transmission, immunity functions, stress response, mitochondrial pathways and neurogenesis were identified. Notably, DEGs from different cell populations overlapped with human ALS-related genes, supporting their potential pathogenic role in specific cell types (Liu et al., 2020).

In 2021, Namboori's group exploited scRNA-seq to analyze the transcriptional profile of MNs differentiated from *SOD1*-mutant iPSCs to study dysfunctional pathways in degenerating MNs. They observed an activation of the TGF-β signaling pathway in *SOD1*-MNs, which may be shared among different ALS forms, demonstrating the utility of sc-transcriptomics in mapping gene regulatory networks associated with MN degeneration (Namboori et al., 2021). An alternative method to scRNA-seq is single nuclei RNA sequencing (snRNA-seq), which allows the specific performance of transcriptomic analysis within the nucleus rather than the entire cell (Fischer and Ayers, 2021). In a recent study, MacLean and colleagues exploited snRNA-seq to analyze the transcriptome of the lumbar portion of the spinal cord of $SOD1^{G93A}$ mice (MacLean et al., 2022). The authors identified a dysregulation of some genes that have already been linked to various ALS-related pathways, including *Epha3* in MNs as well as *Cdh22* and *Cav2* in astrocytes (Cooper-Knock et al., 2021; Daoud et al., 2011; Uyan et al., 2013). Furthermore, the increased transcriptional activity of *Pparg* identified in astrocytes, already described in previous studies on ALS patients, might support an attempt at remyelination (Azizidoost et al., 2022; Kıray et al., 2016; MacLean et al., 2022). Regarding microglia, the transcriptional alterations support the transition toward a proinflammatory phenotype in $SOD1^{G93A}$ mice at 90 days. Furthermore, MacLean's group found an upregulation of the *Sparc* and *Clu* genes, which are involved in synapse dynamics, and *Fos*, which is thought to be a regulator of *Clu* (Chen et al., 2021; Groves et al., 2018; Jones et al., 2011).

Finally, leveraging snRNA-seq technology, Saez-Atienzar identified nine subtypes of GABAergic interneurons and oligodendrocytes that may play a central role in ALS pathogenesis (Saez-Atienzar et al., 2021). Overall, the advent and rapid development of sc-RNA sequencing approaches strongly contributed to a deep understanding of the heterogeneous cellular basis of ALS.

5. miRNAs

Noncoding RNAs (ncRNAs) are ribonucleotide molecules that do not have coding potential but exert regulatory activity in multiple biological processes, including several molecular pathways associated with neurodegeneration (Salta and De Strooper, 2017; Wu and Kuo, 2020). This heterogeneous family of transcripts encloses long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and miRNAs. In particular, miRNAs are small ncRNAs (21–23 nucleotides) that regulate post-transcriptional gene expression. MiRNAs play a key role in cell homeostasis by base pairing with their target mRNAs, thereby reducing protein synthesis by mRNA destabilization or the repression of mRNA translation (Bartel, 2018).

Growing evidence suggests that altered miRNA expression can be linked to different neurodegenerative disorders, including ALS (Gershoni-Emek et al., 2018; Godlewski et al., 2019; Haramati et al., 2010; Liu et al., 2022). Alterations in miRNA metabolism and function can affect crucial biological processes associated with neurodegeneration, such as neurogenesis, neurite outgrowth, apoptosis, autophagy, neuroinflammation and blood–brain barrier (BBB) permeability. Notably, a common subset of miRNAs, including miR-9–5p, miR-21–5p, miR-29 family members, miR-132–3p, miR-124–3p, miR-129–1, miR-146a-5p, miR-155–5p and miR-223–3p, were identified as being dysregulated among different neurological disorders, revealing functional overlap across diseases (Juźwik et al., 2019; Loffreda et al., 2020).

In fact, the major ALS causative genes play critical roles in different aspects of RNA metabolism (Butti and Patten, 2019). Indeed, both TDP-43 and FUS are RNA/DNA-binding proteins involved in multiple steps of RNA processing, including miRNA biogenesis (Lagier-Tourenne et al., 2010; Pham et al., 2020). In particular, TDP-43 promotes neuronal outgrowth through the regulation of miRNA processing (Buratti et al., 2010; Kawahara and Mieda-Sato, 2012; Paez-Colasante et al., 2020), while FUS dysfunctions seem to affect miRNA biogenesis and

miRNA-mediated gene silencing (Dini Modigliani et al., 2014; Morlando et al., 2012; Zhang et al., 2018). Although SOD1 is not an RNA/DNA-binding protein, it presents functions analogous to those of TDP-43 and FUS, such as a propensity for mislocalization, aggregation, and RNA-regulatory functions (Bunton-Stasyshyn et al., 2015; Butti and Patten, 2019; Gal et al., 2016; Pham et al., 2020). Regarding *C9orf72*, its HRE located within the noncoding portion induces aberrant RNA *foci* accumulation with the sequestration of several RBPs, including TDP-43 and FUS, which cause alterations in RNA metabolism (Lee et al., 2013; Mori et al., 2013).

5.1. Dysregulation of miRNAs in ALS

In recent decades, the identification of miRNA dysregulation in biological samples from ALS patients as well as from in vitro and in vivo disease models has led to a deeper understanding of the molecular mechanisms underlying ALS pathogenesis (Table 3).

The dynamic role of miRNAs in multiple steps of neurogenesis has been investigated in several studies (Lang and Shi, 2012). In particular, miR-9, miR-124 and miR-19a/b seem to be involved in promoting the generation of new neurons from neural stem cells and progenitors (Marcuzzo et al., 2014; Vaz et al., 2021; Zhou et al., 2018). In addition, miR-124 seems to have a key role in astrocyte differentiation in SOD1

Table 3
Dysregulation of miRNAs in ALS.

miRNA	Sample	Up/Down regulation	Target/Pathway	References
miR-206	$SOD1^{G93A}$ mice	Up	Neuromuscular synapses and NMJ, HDAC4	Williams et al. (2009)
miR-9	$SOD1^{G93A}$ mice	Up	Neurogenesis, NSCs proliferation, distribution and differentiation	Zhou et al. (2013)
miR-155	$SOD1^{G93A}$ mice	Up	Neuroinflammation	Butovsky et al. (2015); Koval et al. (2013)
miR-125b	$SOD1^{G93A}$ mice	Up	Neuroinflammation	Parisi et al. (2016)
miR-193b-3p	$SOD1^{G93A}$ mice NSC-34 cell	Down	TSC1/mTOR signaling	Li et al. (2017)
miR-183–5p	$SOD1^{G93A}$ mice	Down	Apoptosis and necroptosis	Li et al. (2020)
miR-126–5p	$SOD1^{G93A}$ mice	Down	Axon degeneration and NMJ dysfunction	Maimon et al. (2018)
miR-124	$SOD1^{G93A}$ mice NSC34 cells	Up Down	Astrocytic differentiation, neurogenesis	Vaz et al. (2021); Zhou et al. (2018)
miR-218	$SOD1^{G93A}$ mice, ALS rat	Up	Modulation of excitatory amino acid transporter 2	Hoye et al., (2018, 2017)
miR-1 ***miR-330*** ***miR-29*** ***miR-133*** ***miR-9***	$SOD1^{G93A}$ mice	Down	Myelination process	Dobrowolny et al. (2015)
miR-9 ***miR-124a*** ***miR-19a*** ***miR-19b***	$SOD1^{G93A}$ mice	Up	Neurogenesis	Marcuzzo et al. (2014)
miR-29a	$SOD1^{G93A}$ mice	Up	ER stress	Nolan et al., (2016, 2014)
miR-375–3p	wobbler mouse	P0 – P20: Up P40: Down	Apoptosis	Rohm et al. (2019)
miR-29b-3p	wobbler mouse	P0 – P20: Up P40: Down	Apoptosis	Klatt et al. (2019)
miR-18b-5p	fALS patients (spinal cord), $SOD1^{G93A}$ mice, NSC-34 cell	Down	Apoptosis	Kim et al. (2020)
miR-146a	sALS patients (spinal cord)	Up	Neurofilaments mRNA regulation	Campos-Melo et al. (2013)
miR-524–5p ***miR-582–3p***		Down		
miR-105 ***miR-9***	sALS patients (spinal cord)	Down	Neurofilaments mRNA regulation	Hawley et al. (2019)
miR-1825	ALS patients (CNS and extra-CNS post-mortem samples)	Down	Regulation of TBCB, TUBA4A, CASP3	Helferich et al. (2018)
miR-b1336 ***miR-b2403***	ALS patients (spinal cord)	Down	Neurofilaments mRNA regulation	Ishtiaq et al. (2014)
miR-155 ***miR-142–5p***	Postmortem spinal cord from ALS patients	Up	Clearance of protein aggregates, neural circuit formation and maintenance and cortical neuron migration	Figueroa-Romero et al. (2016)
let-7e ***miR-148b-5p*** ***miR-577*** ***miR-133b*** ***miR-140–3p***		Down	Cell death, immunological responses, neuroinflammation, brain development	
miR-494–3p	C9orf72-ALS iAstrocytes	Down	Regulation of SEMA3A, axonal maintenance, motor neuron degeneration	Varcianna et al. (2019)
miR-375	iPSC-derived human FUS-MNs	Down	ELAVL4, apoptosis	De Santis et al. (2017)
miR-34a-5p ***miR-504–5p***	iPS-derived human ALS-MN progenitors	Down	p53 pathway, apoptosis, synaptic vesicle regulation	Rizzuti et al. (2018)
miR-129–5p	PBMC of sALS patients $SOD1^{G93A}$ mice	Up	ELAVL4/HuD	Loffreda et al. (2020)
miR-34a-5p ***miR-34a-3p*** ***miR-335–5p*** ***miR-335–3p*** ***miR-625–3p***	iPS-derived human ALS MNs, ALS MN-derived EVs	Up/Down	Apoptosis, axon guidance, synaptic plasticity, autophagy, neuroinflammation, intercellular communication	Rizzuti et al. (2022)

mice (Zhou et al., 2018). In the context of the pathological link between MNs and astrocytes, the release of miR-218 from dying MNs and its uptake into astrocytes drives the loss of the astrocytic glutamate transporter EAAT2/Glt1, promoting excitotoxicity and neuroinflammation (Hoye et al., 2018).

Several studies have supported the impact of neuroinflammation on ALS pathogenesis (Liu and Wang, 2017). Particularly, different analyses performed on SOD1^{G93A} mice identified an upregulation of a subset of miRNAs involved in neuroinflammatory pathways, including miR-125b and miR-155 (Butovsky et al., 2015; Koval et al., 2013; Parisi et al., 2016). Beyond in vivo studies, an upregulation of miR-155 and miR-142–5p together with reductions in let-7e, miR-148b-5p, miR-577, miR-133b and miR-140–3p have been found in postmortem spinal cord samples from a small cohort of Caucasian sALS subjects (Figueroa-Romero et al., 2016).

The generation of neuronal cytoplasmic inclusions containing neurofilament light (NFL), medium (NFM), and heavy (NFH) as well as peripherin represents one of the main neuropathological features of ALS (He and Hays, 2004; Hirano et al., 1984; Keller et al., 2012; Kondo et al., 1986; Xiao et al., 2006). It has been demonstrated that several miRNAs regulate *NEFL* mRNA levels, which may control its selective accumulation in ALS patients (Campos-Melo et al., 2013; Hawley et al., 2019; Ishtiaq et al., 2014). Specifically, miR-105 and miR-9 levels were reduced in the spinal cord of sALS patients, although only miR-105 directly interacts and regulates intermediate filament mRNA, supporting the key role of this miRNA in the alteration of neurofilament mRNA metabolism during the disease (Hawley et al., 2019). Furthermore, according to other studies among miRNAs that directly regulate *NEFL* mRNA, miR-146a, miR-524–5p, miR-582–3p, miR-b1336 and miR-b2403 were altered in the spinal cord of ALS patients, suggesting their involvement in the formation of neurofilament aggregates (Campos-Melo et al., 2013; Ishtiaq et al., 2014).

It is well recognized that miRNAs exert a crucial role in the regulation of cell death, which contributes to triggering MN degeneration in ALS (Dahlke et al., 2015; Gagliardi et al., 2019; Martin, 2000; Rohm et al., 2019). Indeed, different groups outlined a deregulation of a subset of miRNAs in the wobbler sALS mouse model. Notably, in the late symptomatic stage of the disease (P40), a decrease in miR-29b-3p and miR-375–3p, which regulate various members of the Bcl2 complex and p53 pathway, was described, whereas at postnatal day 0 (P0) and P20, these miRNAs were found to be significantly upregulated (Klatt et al., 2019; Rohm et al., 2019). MiR-375–3p can prevent apoptosis; thus, its significant downregulation could enhance P53 expression, promoting apoptosis (Bhinge et al., 2016; De Santis et al., 2017; Wang et al., 2018). A downregulation of miR-375 was also described in iPSC-derived MNs with *FUS* mutations, leading to an aberrant increase in its targets, including the neural RNA-binding protein *ELAVL4*/HuD, as well as apoptotic factors (De Santis et al., 2017). *ELAVL4*/HuD is predominantly expressed in neurons, regulating mRNA metabolism. Indeed, decreased expression of *ELAVL4*/HuD impairs neurite formation (Loffreda et al., 2020). In addition to miR-375, *ELAVL4*/HuD is also targeted by miR-129–5p, which has been identified as increased in SOD1^{G93A} mice and in the peripheral blood cells of sALS patients (Loffreda et al., 2020). Several in vivo studies highlighted the upregulated expression of miR-206, miR-218 and miR-29a, which are involved in multiple pathways associated with neurodegeneration, such as the regeneration of neuromuscular synapses, astrocyte dysfunction and ER stress (Nolan et al., 2016, 2014; Williams et al., 2009). Nevertheless, several studies have revealed the role of neuronal miRNA downregulation in ALS-related SOD1 models. In fact, a downregulation of miR-183–5p was described in SOD1^{G93A} mice, promoting apoptosis and necroptosis by targeting *PDCD4* and *RIPK3*. Indeed, miR-183–5p regulates MN survival under stress conditions, and its knockdown induces neuronal death (Li et al., 2020). Moreover, Kim's group found that miR-18b-5p was downregulated in SOD1 mice and in the spinal cord of SOD1 mutant carriers, providing evidence that this miRNA enhances apoptotic cell death through the regulation of *Hif1α*, *Mef2c*, miR-206, *Mctp1* and *Rarb* (Kim et al., 2020).

Recently, our group described for the first time a dysregulation of some miRNAs that regulate genes implicated in biological pathways associated with neurodegeneration. Specifically, we identified decreased levels of miR-34a and miR-504 in iPSC-derived MN progenitors from fALS and sALS patients (Rizzuti et al., 2018). Notably, the dysregulation of miR-34a has been confirmed in both iPSC-derived fully differentiated MNs and secreted exosomes from patients carrying *C9orf72*, *SOD1* or *TARDBP* mutations, together with a dysregulation of miR-335 and miR-625–3p (Rizzuti et al., 2022). The expression levels of miR-34a, miR-335 and miR-625–3p were also assessed in the CSF of ALS patients to explore their potential as disease biomarkers.

5.2. miRNAs as disease biomarkers

To date, clinical heterogeneity among ALS patients and the shortage of disease-specific biomarkers have hampered improvements in diagnosis, prognosis, and the monitoring of disease progression and therapeutic response. Indeed, the identification of promising biomarkers in ALS is truly challenging since an ideal biomarker should be highly specific and sensitive in distinguishing patients from healthy controls or from individuals affected by other neurological disorders. Notably, the discovery of reliable biomarkers may allow patient stratification into more clinically homogeneous cohorts for the development of more effective clinical trials. In recent years, different studies performed on multiple biological samples, such as muscle biopsy, blood and CSF samples from ALS patients (Table 4), have assessed the potential of miRNAs as disease biomarkers (Liu et al., 2022; Ricci et al., 2018). The CSF may represent the most suitable biological fluid to investigate due to its proximity to the CNS and thus to its accuracy in mirroring neurological conditions. Another approach that could complement or eventually replace the use of CSF as a biofluid is the specific enrichment of neuronally derived plasma extracellular vesicles (EVs). Here, comprehensive longitudinal studies are needed to determine the degree of correlation between analytes present in plasma-neuronal EVs and those present in CSF. Some of the most relevant studies performed on miRNAs in blood and CSF are summarized in Table 3. Considering the role of skeletal muscle in ALS pathogenesis and the value of muscle biopsies for monitoring disease progression, specific circulating muscle miRNAs (myo-miRNAs) have been investigated as potential biomarkers (Table 4). Indeed, the advantages of circulating myo-miRNAs include their detectability and stability in body fluids, which allow accurate measurement of their expression levels (Weber et al., 2010). In addition, circulating myo-miRNAs can interact with every tissue in the body. However, the use of blood as a biological sample represents a roadblock given the impossibility of determining the source of circulating miRNAs. The use of more targeted sampling, such as immunopurified specific pools of exosomes/EVs using specific markers, represents a potential solution. In this context, the assessment of miRNA levels in EVs in the blood and/or CSF would represent an easier and relatively noninvasive way to formulate an accurate diagnosis and prognosis (Olejniczak et al., 2018; Wang and Zhang, 2020). Exosomes are small EVs that can be easily isolated from biological fluids and whose relevance is increasingly being recognized in ALS (Gagliardi et al., 2021). RNA sequencing of exosomes isolated from CSF patients identified expression changes in genes involved in several dysregulated processes already described in ALS, including the ubiquitin—proteasome pathway, the oxidative stress response and the unfolded protein response (Otake et al., 2019).

Overall, these results provide significant insights into the role of miRNAs in ALS pathogenesis, supporting the role of miRNAs as diagnostic and prognostic biomarkers (Joilin et al., 2019; Wang and Zhang, 2020). However, conflicting results from the available literature and scarce reproducibility of findings still hamper their use in clinical practice for ALS diagnosis and clinical management, underlining the need to test larger and more homogenous cohorts of samples.

Table 4
miRNAs as biomarkers in ALS.

Sample	Upregulated miRNAs	Downregulated miRNAs	References
CSF	miR-27b, miR-99b, miR-146a, miR-150, miR-328, miR-532–3p		Butovsky et al. (2012)
CSF	miR-143–5p, miR-574–5p	miR-132–3p, miR-132–5p, miR-143–3p	Freischmidt et al. (2013)
CSF	miR-338–3p		De Felice et al. (2014)
CSF	miR-181a-5p	miR-15b-5p, miR-21–5p, miR-148–3p, miR-195–5p, let7a-5p, let7b-5p, let7f-5p	Benigni et al. (2016)
CSF	miR-9–5p, miR-27b-3p miR-124–3p, miR-125b-2–3p, miR-127–3p, miR-143–3p	miR-16–5p, miR-28–3p, miR-92a-5p, miR-142–5p, miR-146a-3p, miR-150–5p, miR-378a-3p, miR-486–5p, let7f-5p	Waller et al. (2017)
CSF	miR-34a-3p, miR-625–3p		Rizzuti et al. (2022)
Monocytes (CD14 + CD16-)	miR-27a, miR-30b, miR-142–5p, miR-155, miR-223, miR-532–3p		Butovsky et al. (2012)
Leukocytes		miR-183, miR-193b, miR-451, miR-3935	Chen et al. (2016)
Leukocytes	miR-9, miR-124a, miR-132, miR-206, miR-338, miR-451a, miR-638, miR-663a, let-7b		Vrabec et al. (2018)
Leukocytes and serum	miR-338–3p		De Felice et al. (2014)
Serum		miR-132–3p, miR-132–5p, miR-143–3p, miR143–5p, let-7b	Freischmidt et al. (2013)
Serum	miR-106b, miR-206		Toivonen et al. (2014)
Serum		miR-1915–3p, miR-3665, miR-4530, miR-4745–5p	Freischmidt et al. (2014)
Serum		miR-1234–3p, miR-1825	Freischmidt et al. (2015a)
Serum	miR-133a, miR-133b, miR-206	miR-27a, miR-146a, miR-149 *	Tasca et al. (2016)
Serum	miR-1, miR-19a-3p, miR-133a-3p, miR-133b, miR-144–5p, miR-192–3p, miR-195–5p	miR-139–5p, miR-320a, miR-320b, miR-320c, miR-425–5p, let-7d-3p	Raheja et al. (2018)
Serum	miR-143–3p, miR-206	miR-374b-5p	Waller et al. (2017)
Serum	miR-142–3p	miR-1249–3p	Matamala et al. (2018)
Serum exosomes		miR-27a-3p	Xu et al. (2018)
Plasma	miR-4649–5p	miR-4299	Takahashi et al. (2015)
Plasma	miR-206, miR-424		de Andrade et al. (2016)
Plasma	miR-206		Sheinerman et al. (2017)
Blood		miR-15a-5p, miR-15b-5p, miR-16–5p, miR-22–3p, miR-23a-3p, miR-26a-5p, miR-26b-5p, miR-27b-3p, miR-28–3p, miR-30b-5p, miR-30c-5p, miR-93–5p, miR-103a-3p, miR-106b-3p, miR-128–3p, miR-130a-3p, miR-130b-3p, miR-144–5p, miR-148a-3p, miR-148b-3p, miR-151a-5p, miR-151b, miR-182–5p, miR-183–5p, miR-186–5p, miR-221–3p, miR-223–3p, miR-342–3p, miR-425–5p, miR-451a, miR-532–5p, miR-550a-3p, miR-584–5p, let-7a-5p, let-7d-5p, let-7 f-5p, let-7 g-5p, let-7i-5p	Liguori et al. (2018)
Muscle	miR-206		Bruneteau et al. (2013)
Muscle	miR-23a, miR-29b, miR-31, miR-206, miR-455		Russell et al. (2013)
Muscle		miR-1, miR-26a, miR-133a, miR-455	Jensen et al. (2016)
Muscle	miR-206, miR-214, miR-424		de Andrade et al. (2016)
Muscle	miR-1, miR-27a, miR-133a, miR-133b, miR-146a, miR-155, miR-206, miR-221		Pegoraro et al. (2017)
Muscle		miR-1, miR-10b-5p, miR-100–5p, miR-133a-3p, miR-133b-3p	Si et al. (2018)
Muscle	miR-10a, miR-99a-5p, miR-100–5p, miR-125a-5p, miR-133a-1/− 2–3p, miR-362, miR-500a-3p, miR-542–5p	miR-26a-1/− 2–5p, miR-150–5p, miR-486–1/− 2–5p, miR-1303–3p	Kovanda et al. (2018)

5.3. miRNA-based therapies

Beyond their potential use as a disease biomarker, the manipulation of miRNA levels by replacing or inhibiting their expression levels may be clinically beneficial. Indeed, support for molecular intervention is largely lacking in ALS. Different studies have supported the value of miRNA-based approaches as attractive therapeutic options (Liu et al., 2022; Wahid et al., 2014). Currently, the two main miRNA-based strategies include antisense technology to inhibit miRNA overexpression or replacement therapy to substitute miRNA deficit in disease (Bai et al., 2019). Delivery methods for miRNA therapy comprise both viral and nonviral systems. Viral-based systems display a high infection efficiency with stable expression of miRNAs or miRNA inhibitors versus nonviral systems. Notably, among AAVs, AAV9 and AAVrh10 promote a very efficient transduction of the CNS, appearing to be very attractive therapeutic options for neurodegenerative disorders. Several attempts at

modulating miRNA expression have been assessed in the SOD1^{G93A} mouse model (Liu et al., 2022). Koval's team explored the therapeutic potential of antagonizing miR-155 in the CNS, demonstrating for the first time that oligonucleotide-based miRNA inhibitors could successfully inhibit miRNA throughout the CNS after intraventricular delivery (Koval et al., 2013). In another study, Nolan's group identified increased miR-29a levels in the spinal cord of SOD1^{G93A} mice during disease progression and assessed the therapeutic effect of miR-29a knockdown in vivo. They reported an increased lifespan in affected ALS male mice after a single intracerebroventricular (ICV) injection of a specific miR-29a antagomir, providing the basis for future therapeutic approaches (Nolan et al., 2014).

Interestingly, multiple studies have shown the role of miR-17–92 family members as master regulators of neurogenesis (Xia et al., 2022). To investigate the therapeutic role of this cluster in ALS, Tung's group overexpressed miR-17–92 in murine SOD1^{G93A} MNs, since they were found to be downregulated in MNs before MN degeneration. Intrathecal injection of adeno-associated virus (AAV) delivering miR-17∼92 improved the motor functions and survival of affected mice, providing insights for the development of future survival-promoting miRNA therapies (Tung et al., 2019).

To date, several studies have supported a significant improvement in survival after the silencing of mutant SOD1 protein in SOD1-linked ALS mice. Stoica and colleagues reported a 50% increase in median survival in SOD1^{G93A} mice and a significant preservation of motor functions after ICV delivery of an AAV9 encoding a specific miRNA designed to target human mutant SOD1 in affected pups (Stoica et al., 2016). In the same years, Borel's team exploited the rAAVrh10 system to systemically deliver an artificial miRNA to silence mutant SOD1 in adult SOD1^{G93A} mice. Significant results in terms of a delay of the disease onset, survival and the preservation of motor functions were obtained in mice as well as a safe silencing of SOD1 in nonhuman primate lower MNs after intrathecal delivery, supporting further investigations on this therapeutic approach toward clinical translation (Borel et al., 2016). Furthermore, it has been demonstrated that intralingual injection of AAVrh10 miR-SOD1 improved respiratory functions in mice (Lind et al., 2020). Since death in ALS patients usually occurs as a result of impaired respiratory function, this approach is worthy of further exploration. The potential efficacy of AAV-delivered miRNA has also been investigated in a *C9orf72* mouse model. At P90, mice were bilaterally injected in the striatum with engineered artificial anti-*C9orf72*-targeting miRNAs able to significantly reduce the accumulation of repeat-containing *C9orf72* transcripts and RNA *foci*, supporting the feasibility of gene therapy (Martier et al., 2019).

Recently, Mueller's team assessed the safety of another gene therapy approach based on a single intrathecal infusion of a clinical-grade AAV-miR-SOD1 in two ALS patients. Preliminary data support the accomplishment of AAV-miRNA delivery, although further studies are needed on the effect of viral vector-mediated therapy for clinical translation (Mueller et al., 2020).

6. Therapeutic and clinical implications of the omics

To date, the restricted therapeutic arsenal for ALS mainly relies on the glutamate receptor antagonist Riluzole and the antioxidant drug Edaravone, which can slow down the disease progression with a moderate impact on disease course. Recently, a combination of Sodium phenylbutyrate and Taurursodiol have been released by FDA since their synergistic action can reduce neuronal cell death and oxidative stress (Tzeplaeff et al., 2023). However, none of these drugs has shown a dramatic change in the natural history of this disease.

The lack of effective therapies for ALS depends on the complex multifactorial etiopathogenesis underlying the disease. Progress in unraveling ALS pathogenesis has been propelled by the discovery of causative genes and disease-modifying targets. Indeed, targeting specific genes through gene therapy approaches may open new therapeutic perspectives leading to the development of new effective drugs.

In the clinical scenario, several therapeutic trials are exploring the effectiveness of ASOs to target *SOD1*, *FUS*, *ATXN2*, and *C9orf72* (Mullard, 2021). Notably, Tofersen, which has received accelerated approval by FDA for the treatment of ALS patients with mutations in *SOD1*, plays a groundbreaking role in the advancement of gene therapy for ALS, being the first ASO employed in patients. Despite its ability to modify the expression of toxic SOD1 protein and decrease plasma NfL, the clinical benefit and long-term effects of this ASO are currently under investigation (Miller et al., 2020, 2022).

The integration of multi-omics approaches may allow to assess the role of multiple pathways dysfunction in neurodegeneration, providing insights for the discovery of new disease biomarkers and the development of efficacious therapeutic strategies (Bu et al., 2016; Castrillo et al., 2018; Hampel et al., 2018a, 2018b; Lam et al., 2020; Olivier et al., 2019; Santiago et al., 2017).

Several studies have already explored the potential of multi-omics strategies in unraveling the molecular complexity of ALS (Mitropoulos et al., 2018; Morello et al., 2020; Vijayakumar et al., 2019). Interestingly, integrative omics approaches may represent a useful tool to stratify ALS patients into clinically relevant subgroups toward the development of new precision diagnostics and therapeutics. A comprehensive molecular analysis of motor cortex samples from affected individuals have revealed how genomic alterations correlate with subtype-specific transcriptional signatures, supporting the interplay between genomic and transcriptomic in shaping the disease pathogenesis (Morello et al., 2019). These findings laid the ground for the identification of new potential targets for genomic-based patient stratification and personalized therapies (Maugeri et al., 2019; Morello et al., 2019, 2017b; Morello and Cavallaro, 2015).

The genetic variability among ALS cases represents a real challenge in developing effective treatments. Despite this complexity, identifying shared pathological features could open new therapeutic possibilities for many patients. The team led by Catanese has developed advanced mathematical and machine-learning tools, along with increased access to deep-sequencing analysis. These tools enabled the integration of multiple biological information, toward the identification of druggable targets as well as diagnostic/prognostic markers (Catanese et al., 2023). They conducted a comprehensive multi-omics analysis encompassing transcriptional, epigenetic, and mutational aspects in human iPSC-derived MNs carrying *C9orf72*, *TARDBP*, *SOD1*, and *FUS* mutations, together with datasets from patient biopsies. Despite gene-specific profiles, a common transcriptional pattern emerged in ALS, characterized by increased stress levels and synaptic abnormalities. WGS linked altered gene expression to methylation profiles, revealing profound epigenetic changes associated with abnormal transcriptional signatures in ALS. Applying multi-layer deep machine-learning to integrate blood and spinal cord transcriptomes uncovered a statistically significant correlation, enriched in toll-like receptor signaling pathways (Catanese et al., 2023).

Neurotrophic factors (NTFs) have been deeply investigated as potential therapeutic targets for ALS since they regulate several physiological processes in the CNS such as neuronal differentiation and survival, axonal outgrowth and synapses maintenance. Indeed, a lot of studies have already demonstrated the protective role of NTFs against motor neuron degeneration both in vitro and in vivo (Gouel et al., 2019; Tovar-Y-Romo et al., 2014). Furthermore, integrative omics analysis identified a similar dysregulation of neurotrophins together with their corresponding receptors in ALS mouse models and patients (Aronica et al., 2015; Morello et al., 2017b; Morello and Cavallaro, 2015). Nevertheless, some concerns in using NTFs for ALS therapy have emerged due to methods of administration, biodistribution, safe dosages, long-term effectiveness and potential combination with other treatments. In this context, the use of innovative delivery systems and small molecules able to mimic NTFs may overcome these limits, providing a promising therapeutic approach for treating ALS (Volonté

et al., 2020). In addition to their trophic role, NTFs are known to regulate glutamate signaling together with other neurotransmitters and neuromodulators including histamine (HA), which is known to regulate multiple neurological functions (Cacabelos et al., 2016; Fukui et al., 2017; Kárpáti et al., 2018). The translational potential of histaminergic modulation is supported by the integration of multi omics data, which revealed a dysregulation at both genomic and transcriptomic levels of multiple genes associated with HA receptors, metabolism, transport, secretion, and signal transduction in distinct ALS subgroups. In this regard, a specific modulation of HA-related pathways has already demonstrated an effectiveness in ameliorating ALS features, both in vivo and in vitro disease models (Apolloni et al., 2019a, 2019b, 2017).

Taken together, all these studies support that the complexity of neurodegenerative disorders, including ALS, typically arise from dysregulation in multiple biological processes (Benchekroun and Maramai, 2019; Geldenhuys and Van der Schyf, 2013; Ramsay et al., 2018, 2016). To address this complexity, new approaches able to simultaneously target multiple proteins and pathways are required to successfully tackle the disease onset and progression. A polypharmacology perspective may help to discover connections between drugs and targets, providing a thorough understanding of how drugs work together with their eventual side effects (Bolognesi and Cavalli, 2016; Villaveces et al., 2015). Besides drug discovery, an integrative approach may also be useful to provide insights for drug repositioning. As a matter of fact, several potential therapeutic molecules that failed at clinical stages because of their low efficacy or toxic pharmacological profile might be reconsidered in drug discovery processes based on the emerging molecular taxonomy of ALS patients derived from omics.

7. Conclusions

In the last decade, omic approaches have yielded invaluable insights into ALS pathogenesis. In particular, genomic techniques have enabled the discovery of new pathogenic genes and novel molecular targets in a noninvasive manner. Despite their limited diagnostic power and poor replicability among independent populations, GWASs together with WGS and WES have revealed the possibility of multiple common risk *loci* associated with ALS. The discovery of an HRE in the *C9orf72* gene as one of the most important genetic causes of ALS has shed light on the role of STR expansions in the etiology of ALS. The concomitance of more than one pathogenic variant in the same individual with fALS has progressively increased the notion of an oligogenic heritability in ALS, but open questions remain on the role of genetic modifiers in contributing to disease onset and phenotype. Furthermore, massive sequencing of exomes and genomes combined with association studies on large patient-control cohorts has dramatically increased the identification of single nucleotide variants associated with ALS.

Beyond genetics, epigenetic mechanisms may be ideal pharmacological targets for prospective therapies in ALS due to the dynamicity and reversibility of epigenetic changes. For instance, blood and neural tissue from ALS patients displayed enhanced DNA methylation and reduced histone acetylation, and ASO therapy targeting HDAC6 rescued impaired axonal transport in *FUS*-ALS patient-derived MNs (Guo et al., 2017).

To date, transcriptomic analyses have elucidated some of the molecular pathways dysregulated in ALS, offering clues for the development of new therapeutics, such as RNA-targeted therapies. Furthermore, innovations in RNA-sequencing technologies have produced a large amount of data that increasingly improved the understanding of molecular mechanisms underlying ALS and enabled the discovery of new potential disease biomarkers. Indeed, the successful implementation of RNA sequencing methodologies has led to the development of sophisticated technologies with single-transcript single-cell resolution through laser capture microdissection or spatial transcriptomic approaches, providing new tools for the identification of genes whose dysregulation is associated with specific cell identity or tissue regional susceptibilities.

Interestingly, miRNAs have provided additional insights into ALS pathogenetic mechanisms (Liu et al., 2022). Thus far, the role of miRNAs in the accurate diagnosis, prognosis or monitoring of ALS progression has been deeply investigated. Despite the impossibility of determining the source of circulating miRNAs, which represents an important limitation, blood is an attractive source of biomarkers. Nevertheless, different miRNA-based studies have often yielded conflicting and poorly reproducible results, to date without the possibility of identifying a specific miRNA signature potentially transferable into clinical practice for diagnostic and prognostic stratification. Although the manipulation of miRNA levels may be clinically beneficial, optimal support for molecular intervention for ALS is still lacking.

Overall, epigenetic mechanisms and posttranscriptional changes associated with neurodegeneration are still entangled, and understanding these concepts is crucial to approach ALS pathogenesis and establish new paths to treatment. In fact, despite promising results and accumulating knowledge on ALS pathomechanisms, a specific disease-modifying treatment is still not available. The complex molecular architecture underlying ALS pathogenesis and the current lack of an effective ALS therapy suggest that successful treatment will be achieved by simultaneously targeting multiple pathways. Greater integration of omic data as well as technological advances may provide better insights into ALS disease pathogenesis, help to improve patient stratification and prognosis through the use of subgroup-specific biomarkers and drive the development of subset-specific therapies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

MR, LS, VM and DG drafted the manuscript with input from all authors. SS, GC, LQ and LB contributed to the conception and design of the manuscript and to the interpretation of relevant literature. LO, DP, FV, AR, NT, SC and GPC critically revised the manuscript for intellectual content. All authors read, contributed to the article, and approved the submitted version.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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