Abstract: Prion diseases are transmissible spongiform encephalopathies (TSEs) caused by a conformational conversion of the native cellular prion protein (PrP\textsuperscript{C}) to an abnormal, infectious isoform called PrP\textsuperscript{Sc}. Amyotrophic lateral sclerosis, Alzheimer’s, Parkinson’s, and Huntington’s diseases are also known as prion-like diseases because they share common features with prion diseases, including protein misfolding and aggregation, as well as the spread of these misfolded proteins into different brain regions. Increasing evidence proposes the involvement of epigenetic mechanisms, namely DNA methylation, post-translational modifications of histones, and microRNA-mediated post-transcriptional gene regulation in the pathogenesis of prion-like diseases. Little is known about the role of epigenetic modifications in prion diseases, but recent findings also point to a potential regulatory role of epigenetic mechanisms in the pathology of these diseases. This review highlights recent findings on epigenetic modifications in TSEs and prion-like diseases and discusses the potential role of such mechanisms in disease pathology and their use as potential biomarkers.

Keywords: epigenetics; DNA methylation; histone modifications; microRNA; prion diseases; prion-like diseases

1. Introduction

Epigenetics is the study of heritable changes in gene activity or function that is not associated with any change in the DNA sequence itself [1]. Three major epigenetic mechanisms have been described: DNA methylation and histone modifications essentially alter the structure of the nearby chromatin of a particular gene or region, whereas non-coding RNAs, especially microRNAs (miRNAs), may regulate expression without the necessity for the physical vicinity for their target genes.

DNA methylation involves the covalent transfer of a methyl group to the C-5 position of the nucleobase cytosine to form 5-methylcytosine. In mammals, DNA methylation may occur at cytosines in any context of the genome [1] and can participate in the regulation of gene expression. Histones are structural proteins that form DNA nucleosomes and are frequently subjected to covalent post-translational modifications. They are involved in the expression and repression of target genes generally via chromatin modification [2]. The most studied histone modifications are acetylation, methylation, and phosphorylation, but also other modifications exist, including citrullination, ubiquitination, ADP-ribosylation, deamination, and proline isomerization [2,3].

MicroRNAs are small non-coding RNAs (21–23 nucleotides in length) that may regulate gene expression at transcriptional, posttranscriptional, or translational levels [4]. Although miRNAs may induce gene expression in some cases by their interaction with
gene promoters [5], miRNA-based regulation is thought to rely largely on the repression of target mRNA translation or its sequence-dependent degradation. Several miRNAs display a cell- or tissue-specific expression profile, while others are widely expressed. They can be found in blood and other biofluids as free (mainly protein-associated) complexes or can be contained by extracellular vesicles. Moreover, circulating miRNAs can be detected and measured by highly sensitive and specific methods (e.g., quantitative PCR and next-generation sequencing). All these characteristics have facilitated studies of miRNAs as potential biomarker molecules [6].

The mentioned epigenetic mechanisms are involved in several aspects of brain development as well as in normal aging [7,8]. DNA methylation and histone acetylation are essential in memory acquisition, learning, and acquisition of long-term memories [8–10], and miRNAs are crucial for the formation and maturation of synapses and for dendritogenesis in early brain development [11–13]. Considering the central role of epigenetics in neural plasticity, it is not surprising that dysregulation of these processes has been associated with different neurodegenerative diseases, either by mediating interactions between genetic and environmental risk factors or by directly interacting with disease-specific pathological factors [7,8]. The neurodegenerative disorders where epigenetics seem to have a key role include Alzheimer’s (AD), Parkinson’s (PD), and Huntington’s (HD) diseases, amyotrophic lateral sclerosis (ALS), prion diseases, stroke, and global ischemia [7,8]. The first four are also known as prion-like diseases because they are proteinopathies that share common pathogenic mechanisms with prion diseases, including the accumulation of misfolded proteins in the central nervous system (CNS) [14,15].

Prion diseases, also referred to as transmissible spongiform encephalopathies (TSEs), are a group of neurodegenerative disorders affecting humans and other animals [16] and are caused by a conformational conversion of the cellular prion protein (PrP⁰) to an infectious isoform, partially resistant to proteases and prone to form aggregates called PrPSc [17].

Research in yeast has revealed that certain proteins that adopt prion conformation, such as URE3 or PSI⁺, can be considered as an epigenetic mechanism that can be inherited through mitosis and meiosis. These self-templating conformations of prion proteins interact with nucleic acids (DNA and RNA) and can regulate gene expression through the modification of chromatin remodeling, nucleic acid translation, and replication, providing beneficial phenotypes in stressful conditions [18]. If prions in yeast possess these characteristics, it could be expected that alteration of the prion protein and other proteins with similar characteristics in mammals will also affect epigenetic mechanisms. Increasing evidence suggests involvement of epigenetic mechanisms in the pathogenesis of prion-like diseases and other neurodegenerative disorders. However, current knowledge about the association of epigenetics with prion diseases is scarce.

Given that some of the affected mechanisms may be shared with TSEs and prion-like diseases, this review summarizes the latest findings on epigenetic modifications in prion-like diseases and reports the recently discovered roles of epigenetic mechanisms in TSEs.

2. Epigenetic Changes in Prion-Like Diseases

2.1. DNA Methylation

2.1.1. DNA Methylation Profiles

Altered DNA methylation patterns have been associated with the neuropathology of prion-like diseases. Several studies have identified sets of genes containing differentially methylated regions (DMRs) and differentially methylated positions (DMPs) between patients and healthy controls, primarily in peripheral blood [19–26] and brain tissue [27–35] and to a lesser extent in saliva [23] and using in vitro models [36,37]. Table 1 summarizes global and gene-specific DNA methylation changes reported in these diseases.

When comparing the DMRs and DMPs identified in each prion-like disease (Supplementary Table S1) using the InteractiVenn software [38], no common DMRs and DMPs were found between all four diseases, but some regions and positions matched...
between two or three of these diseases (Figure 1). Regarding the DMRs, the disease pairs that shared the highest number of common regions were first PD and HD, second PD and ALS, and third PD and AD (Figure 1a). On the other hand, PD and AD are the only diseases that share a relatively high number of DMPs (Figure 1b). Although these comparisons between the DMRs and DMPs identified in prion-like diseases allow an overview of common differentially methylated genes shared between some of these diseases, there are limitations that could affect the number of regions and positions identified in each disease and must be taken into account: (1) the compared studies were performed in different tissues and body fluids which could lead to different methylation profiles inherent to each tissue; (2) the number of studies developed in each disease is different, being AD and PD the most studied ones; and (3) the methodology used in the different works varies. Most studies were performed using the 450 K methylation array, and whole genome bisulfite sequencing was used only in one study of PD [37]. This methodology detects DMPs in non-annotated sequences such as lincRNAs, pseudogenes, and antisense or unknown miRNAs, which explains in part why the number of DMPs and DMRs in PD is substantially higher than in other diseases.

![DMRs in prion-like diseases](image1.png)  ![DMPs in prion-like diseases](image2.png)

**Figure 1.** Comparison of differentially methylated regions (DMRs) and positions (DMPs) in prion-like diseases. Venn diagrams indicate the number of common and unique DMRs (a) and DMPs (b) in AD, PD, ALS, and HD.

Studies on the DNA methylation process have concentrated on different areas of the CNS depending on their relevance with the pathogenesis of each disease. Epigenome-wide studies on AD patients have identified DMRs in the superior temporal gyrus, a region that displays a marked gene dysregulation in AD [27,28]. Most of these DMRs were found to be in gene promoters and associated with AD pathology. Significant DNA methylation changes are also found in PD-affected brain areas, namely the dorsal motor nucleus of the vagus, substantia nigra, and cingulate gyrus [32]. In HD, DNA methylation studies performed so far have shown disparate results. A genome-wide DNA methylation profile of cortex tissues from HD patients suggests that DNA methylation may have a minimal association with HD status but could be correlated with the age of disease onset and contribute to the tissue-specific expression patterns of huntingtin (HTT) [39]. In contrast, using the same methodology but analyzing multiple CNS regions, another study identified 11 co-methylation modules associated with HD status in cortical regions and observed an accelerated epigenetic age in specific brain regions (frontal lobe, parietal lobe, and cingulate gyrus) of HD patients [35], measured by combining DNA methylation levels of known CpGs [40].

Genome-wide studies have detected DNA modifications in specific genes that have been analyzed in detail to elucidate their role in neurodegeneration. Epigenetic control of enhancers seems to be involved in AD as loss of CpH (most frequently at CpA sites)
methylation of enhancers, which is normal in aging neurons but is accelerated and occurs early in AD neurons. This modification seems to prompt the reactivation of cell cycle and neurogenesis pathways and, in the case of the enhancer of DSCAML1 that codes for Down Syndrome cell adhesion molecule-like protein 1, precedes the onset of neurofibrillary tangle pathology [41]. Hypomethylation of DSCAML1 gene enhancer is associated with an upregulation of BACE1 (beta-secretase 1) transcripts and an increase in amyloid plaques, neurofibrillary tangles, and cognitive decline [41]. These results support an early involvement of epigenetic changes in AD.

In the same disease, a protective role has been suggested for PM20D1 (peptidase M20 domain containing 1). DNA methylation and RNA expression of this gene are associated with AD, and its overexpression in cells is neuroprotective against AD stressors [42].

Methylation changes in other genes have been related to prion-like disease pathogenesis, although its role is still unknown. In PD, patients show hypomethylation of the promoter region of SNCA, the gene encoding α-synuclein protein [43]. Moreover, several ALS-related genes (DENND11, COL15A1, TARDBP, RANGAPI, and IGHMBP2) and DNA repair genes (OGG1, APEX1, PNKP, and APTX) are differentially methylated in ALS patients [44–46]. Differential DNA methylation has also been observed in specific genes in HD, namely HES4, a transcription factor involved in neural stem cell regeneration, and BDNF, encoding brain-derived neurotrophic factor [47,48]. HES4 promoter hypermethylation is associated with reduced expression of the gene and with striatal degeneration and age of onset of HD patients. Consistently, inhibition of HES4 by shRNA increases mutant HTT aggregates in a cell model of the disease. BDNF promoter hypermethylation in the blood of HD patients did not correlate with motor or cognitive status but may represent a biomarker for HD-associated psychiatric symptoms.

Most of the reported studies reveal that changes in DNA methylation can be associated with pathogenic processes of these neurodegenerative diseases, but there does not appear to be a universal mechanism relating DNA methylation and protein aggregates. Studies performed in human patients are normally carried out at the late stages of the disease when it is difficult to differentiate if changes in DNA methylation are a cause or a consequence of neurodegeneration. Analysis of this epigenetic process in animal or cellular models could possibly allow us to elucidate this question.

A limitation of most of these studies is the technology used for the determination of DNA methylation. Methylation arrays or NGS-sequencing-based methods did not differentiate between methyl Cytosines (mC) and their oxidized product hydroxymethyl Cytosines (hmC), which has regulatory functions and could be an epigenetic mark in its own right [49]. Antibody-based techniques have already been used in these diseases to specifically detect 5mC and 5hmC methylation forms [50,51]. However, these techniques cannot identify specific genes of interest. Third-generation sequencers [52] could help elucidate which epigenetic mark is involved in a gene-specific regulation.

2.1.2. Biomarkers Based on DNA Methylation

DNA methylation as a potential biomarker has been investigated in easily accessible tissues at both genomic and gene-specific levels. Both sporadic (SALS) and familial ALS (FALS) patients show increased global 5-methylcytosine levels in blood DNA [53]. At the gene level, hypermethylation of the promoter for C9orf72, a gene responsible for the majority of the FALS cases (as well as for those of frontotemporal dementia), correlates with its reduced mRNA expression levels in a clinical cohort of C9orf72 pathological expansion carriers [54]. A significant association between DNA methylation age-acceleration, disease duration, and age of onset has also been observed in C9orf72 carriers [55]. The second most common cause of FALS is mutations in superoxide dismutase 1 (SOD1), with nearly 200 mutations described, some of which show incomplete penetrance and great phenotypic variability. ALS patients carrying not fully penetrant SOD1 mutations display an increase in global DNA methylation, and DNA methylation levels correlate positively with disease duration [56]. However, since the promoters of four major ALS genes (C9orf72, SOD1,
TARDBP, and FUS) were not methylated in the study subjects, it was concluded that the increased methylation is likely to occur in other gene regions. In this study, no repeat expansion was observed in C9orf72, which supports the previous finding [51] that gene-specific methylation in the C9orf72 locus is dependent on this pathological feature.

In contrast, DNA hypomethylation seems to be a key mark in PD patients, finding several hypomethylated and upregulated genes in blood and saliva samples associated with systemic immune response pathways and mitochondrial dysfunction [21,23]. In addition, in leukocytes from PD patients, hypomethylation of Npas2 (neuronal PAS domain protein 2) [57] and DRD2 (dopamine receptor D2) [57] has been proposed as a novel biomarker for PD.

In blood from AD patients, B3GALT4 (beta-1,3-galactosyltransferase 4), a gene associated with AD onset and progression, and PTGR3 (prostaglandin reductase 3), associated with AD risk, are hypomethylated and correlate with memory performance and cerebrospinal fluid (CSF) levels of Aβ and tau [58]. Moreover, hypomethylation of BIN1 (bridging integrator 1), a gene associated with AD pathogenesis, and hypermethylation of estrogen receptor α (ESR1) gene promoter, which is related to impaired cognitive function and quality of life of AD patients, have been also reported [59,60]. Another potential biomarker of this disease could be the hypomethylation in TOMM40 (translocase of outer mitochondrial membrane 40) and APOE (apolipoprotein E) gene promoters observed in the hippocampus, cerebellum, and peripheral blood of AD patients, which correlated with increasing APOE and decreasing TOMM40 expression [61]. Besides these promising results, very few have been subjected to clinical trials. Only methylation levels on COASY (Coenzyme A synthase) and SPINT1 (Serine peptidase inhibitor Kunitz type 1) promoter regions have been considered convenient and useful biomarkers for AD [62].

In HD, DNA methylation status in peripheral blood does not seem to be affected as, after a microarray study of blood samples, no distinctive patterns were observed in the covered CpG sites and their associated genes [25].

2.1.3. In Vitro Studies

Cellular models are particularly useful for analyzing the effect of DNA methylation and investigating the role of methylation in candidate genes and potential treatments. DNA methylation changes in prion-like diseases have been investigated in vitro using cell models. A whole-genome bisulfite sequencing study using induced pluripotent stem cell (iPSC) -derived dopaminergic neurons from sporadic PD and monogenic LRRK2 (Leucine-rich repeat kinase 2)-associated PD patients revealed global DNA hypermethylation associated with disease [37], conversely to the hypomethylation observed in blood and saliva. In ALS, a study that evaluated the methylation status of human embryonic stem cells (hESCs) and iPSCs both carrying the C9orf72 mutation showed that hESCs were completely unmethylated at the C9orf72 repeats, whereas iPSCs were hypermethylated. This methylation status remained unchanged after the differentiation of hESCs and iPSCs into neural precursors. The hypermethylation observed in the C9orf72 repeats of iPSCs was proposed as a possible neuroprotective mechanism attenuating the accumulation of potentially toxic repeat-containing mRNAs in neurons, given that hESCs presented a more severe phenotype than iPSCs [63].

Hypomethylation of the SNCA gene has been described in early onset PD patients [43], and lowered methylation status is likely to increase SNCA expression, contributing to the accumulation of α-synuclein in this disease. With the purpose of maintaining normal physiological levels of α-synuclein, Kantor et al. [64] experimentally methylated the SNCA gene using a system based on CRISPR-deactivated Cas9 fused with the catalytic domain of DNMT3A (DNA methyltransferase 3 alpha). This technique was applied to iPSC-derived dopaminergic neurons from a PD patient resulting in hypermethylation of the SNCA gene, downregulation of the SNCA expression, and a reversion of disease-related phenotypic perturbations [65]. The same hypermethylation-based approach has been recently used to manipulate the levels of amyloid-beta (Aβ) precursor (APP) in cultured neurons from AD mice, resulting in decreased Aβ peptide levels, decreased Aβ42/40 ratio, and increased
cell survival [66]. Importantly, further studies in vivo indicated that lentiviral injection of dCas9-Dnmt3a in mouse brain induces efficient DNA methylation editing, decreases the levels of APP, and improves the cognitive defects associated with this AD model.

2.1.4. Mitochondrial DNA Methylation

Finally, in addition to nuclear DNA, mitochondrial DNA (mtDNA) methylation has also been observed in humans and animal models. In ALS, SOD1 mutation carriers display increased levels of mtDNA and demethylation of the mitochondrial D-loop, a noncoding region critical for both mtDNA replication and transcription. This could represent an attempt to compensate for the disease-associated loss of mitochondrial function by mtDNA upregulation in carriers of ALS-linked SOD1 mutations [67]. While D-loop is also hypomethylated in the hippocampus of a mouse model of AD (APP/PS1), this is associated with decreased mtDNA copy number [68]. Thus, while altered methylation of mtDNA suggests a possible role for this epigenetic mechanism in ALS and AD, the fact that the outcome in the level of mtDNA is opposite in the two cases warrants further studies on the topic.

### Table 1. Global and gene-specific DNA methylation in prion-like diseases.

| Disease                     | Species/Model           | Tissue Type                          | Methylation Finding                                                                 | References |
|-----------------------------|-------------------------|--------------------------------------|-------------------------------------------------------------------------------------|------------|
| Alzheimer’s disease         | Human                   | Brain, peripheral blood              | Methylation profiles of AD patients. Identification of differentially methylated positions (DMPs) | [19,20,30,31] |
|                             | Human                   | Brain                                | Methylation profile of AD patients. Identification of differentially methylated regions (DMRs) | [27]       |
|                             | Human                   | Superior temporal gyrus              | Hypermethylated DMRs                                                                | [28,29]    |
|                             | APP/PS1 mice            | Hippocampus                          | Changes in mitochondrial DNA methylation                                           | [68]       |
|                             | Human                   | Neurons                              | Hypermethylated enhancers in DSCAML1 gene                                           | [41]       |
|                             | Human                   | Hippocampus, cerebellum, peripheral blood | Hypomethylation in TOMM40 and APOE gene promoters                                 | [61]       |
|                             | Human                   | Frontal cortex                       | Methylation of PM20D1 gene                                                          | [42]       |
|                             | Human                   | Peripheral blood                     | Hypomethylation of B3GALT4 and ZADH2 genes                                          | [57]       |
|                             | Human                   | Peripheral blood                     | Hypomethylation of BIN1 gene                                                        | [58]       |
|                             | Human                   | Peripheral blood                     | Hypermethylation of ERα gene promoter                                               | [59]       |
|                             | Human                   | Peripheral blood, iPSC-derived dopaminergic neurons | Global DNA hypermethylation changes                                               | [36,37]    |
|                             | Human                   | Peripheral blood, saliva             | Global DNA hypomethylation changes                                                 | [21,23]    |
|                             | Human                   | Peripheral blood, iPSC-derived dopaminergic neurons | Hypomethylation of SNCA gene promoter. Reversion of disease symptoms via CRISPR/Cas9-mediated SNCA hypermethylation | [43,65]    |
|                             | Human                   | Leukocytes                           | Hypomethylation of NPAS2 and DRD2 genes                                             | [60,63]    |
|                              | Human                   | Peripheral blood                     | Methylation profile of ALS patients. Identification of DMPs                         | [24]       |
|                              | Human                   | Brain                                | Methylation profile of ALS patients. Identification of DMRs                         | [33]       |
|                              | Human                   | Peripheral blood                     | Increased global 5-methylcytosines levels in sALS and FALS                          | [53]       |
| Amyotrophic lateral sclerosis| Human                   | Peripheral blood                     | Hypermethylation of the C9orf72 promoter and association of DNA methylation age-acceleration with disease duration and age of onset in C9orf72 expansion carriers | [54,55]    |
|                              | Human                   | Peripheral blood                     | Increase in global DNA methylation and demethylation of the mitochondrial D-loop region in SOD1 mutation carriers | [56,57]    |
|                              | Human                   | hESCs, iPSCs                         | hESCs unmethylated and iPSCs hypermethylated at the C9orf72 repeats                 | [64]       |
|                              | Human                   | Brain, motor neurons                 | Differential methylation of KIAA1147, IGHMBP2, COL15A1, TARDBP, RANGAP1, IGHMBP2, OGG1, APEX1, PNKP, and APTX | [44–46]    |
Table 1. Cont.

| Disease                  | Species/Model | Tissue Type | Methylation Finding                                                                 | References |
|--------------------------|---------------|-------------|--------------------------------------------------------------------------------------|------------|
| Huntington’s disease     | YAC128 mice   | Brain       | Methylation profile. Identification of DMRs                                          | [34]       |
|                          | Human         | Peripheral blood | Methylation profile of HD patients. Identification of DMPs                          | [26]       |
|                          | Human         | Brain       | Minimal association of DNA methylation with HD status                                | [39]       |
|                          | Human         | Peripheral blood | No significant changes between patients and controls                                  | [25]       |
|                          | Human         | Brain       | 11 co-methylation modules associated with HD status                                  | [35]       |
|                          | Human         | Brain       | HES4 promoter hypermethylation                                                        | [47]       |
|                          | Human         | Plasma, saliva | BDNF promoter hypermethylation                                                       | [48]       |

2.2. Histone Modifications

The most studied histone modification in prion-like diseases is acetylation. Global levels of acetylated histones and differential expression of the enzymes in charge of their acetylation or deacetylation have been related to the pathology of these diseases. Moreover, pharmacological modulation of these enzymes could ultimately result in a potential treatment strategy. Table 2 summarizes the main results in this subject.

Widespread acetylome variation has been observed in different brain areas of AD patients, and this epigenetic modification can be induced by pathological tau [69,70]. Acetylation of a lysine residue in histone 3 (H3K27) varies in the vicinity of several known AD risk genes (APP, CR1, MAPT, PSEN1, PSEN2, and TOMM40) and is robustly associated with the disease [69]. Similarly, altered histone acetylation has been linked to PD-associated neurodegeneration. PD neurotoxins specifically increase histone acetylation through an autophagy-mediated reduction of histone deacetylases (HDACs) in PD patients’ dopaminergic neurons [71].

The modulation of epigenetic enzymes involved in acetylation, mainly HDACs, also has a role in the development and progression of prion-like diseases. HDACs can be divided into four subtypes, classes I, II, and IV being classical HDACs and class III consisting of NAD+ -dependent silent information regulator 2 family members (sirtuins). HDAC activities are unbalanced in fibroblasts from PD patients, which is associated with impaired mitophagy and increased cell death [72].

In addition, changes in expression levels of particular HDACs have been described, but their modifications are not always in accordance with studies. Modifications can be different depending on the disease and CNS cell populations. HDAC1 and HDAC2 levels are strongly decreased in the frontal cortex of AD patients, and HDAC1 is also reduced in the hippocampus [73]. HDAC2 downregulation seems to contribute to cholinergic nucleus basalis of Meynert neuronal dysfunction, neurofibrillary tangles pathology, and cognitive decline during the clinical progression of AD [74]. On the contrary, HDAC2 is upregulated in the microglia from the substantia nigra of PD patients [75]. Additionally, nuclear accumulation of HDAC4, which is normally localized at the cytoplasm, seems to promote neuronal apoptosis in PD-affected dopaminergic neurons [76].

The levels of class II HDACs (4, 5, and 6) are increased in the skeletal muscle of SOD1-ALS mice with severe neuromuscular impairment [77]. Although this increase was not observed in motor neurons, Class II HDACs could also contribute to motor neuron degeneration as their pharmacological inhibition is able to restore the expression and function of glutamate transporter EAAT2 in the spinal cord of ALS [78]. However, HDAC4 expression is decreased in the skeletal muscle of ALS patients [79], and the skeletal muscle-specific ablation of HDAC4 is sufficient to induce an earlier onset of the disease, a decrease in neuromuscular junctions’ size, and muscle denervation and atrophy in SOD1-ALS mice [80]. Finally, an in vivo brain assessment of HDAC alterations by positron emission tomography showed no significant differences in HDAC expression levels between ALS patients and healthy controls [81], suggesting that HDAC alterations may have a more profound effect on the disease in peripheral tissues. Given that the skeletal muscle function is compromised in ALS, the implication that HDAC4 could be protective in ALS skeletal muscle.
muscle has questioned the use of broad-range HDAC inhibitors as a strategy for ALS treatment [82]. However, research on the role of HDACs in different tissues warrants further investigation because the discovery of highly selective inhibitors for HDACs could eliminate the potential negative effects of more broad-range targeting in the future.

In AD patient-derived neurons and triple transgenic (3xTg-AD, carrying mutated forms of APP, PSEN1, and MAPT/tau) mouse model, inhibition of HDAC3 (Class I) decreases pathological tau phosphorylation and acetylation, reduces Aβ protein expression, increases Aβ degradation, improves learning and memory and normalizes several AD-related genes [83]. Importantly, HDAC6 seems to influence tau phosphorylation, autophagic flux, and tubulin acetylation [84], and its inhibition stimulates pathological tau degradation in ADLP APT mice (carrying six mutations in APP, PSEN1, and MAPT/tau) and AD patient-derived brain organoids [85]. The inhibition of HDAC6 has also been proposed as a therapeutic strategy for PD, as this enzyme contributes to oxidative injury and dopaminergic neurotoxicity through mediating deacetylation of peroxiredoxins 1 and 2 in oxidopamine-induced PD mice [86]. In the PD mouse model expressing mutated LRRK2 (R1441G), HDAC inhibition by valproic acid has a neuroprotective effect through modulation of neuroinflammation and improvement of PD-like symptoms [87]. Inhibition of histone sirtuin-2 deacetylase (SIRT2) also has therapeutic effects protecting degenerating dopaminergic neurons, reducing microglia activation, and facilitating the trafficking and clearance of misfolded proteins [88,89].

This therapeutic approach of HDAC inhibition has also been investigated in ALS models. HDAC inhibition in spinal cord-dorsal root ganglion cultures enables the heat shock response, which manages a load of aberrant proteins in a stress-dependent manner in cultured spinal motor neurons and also rescues the DNA repair response in iPSC-derived motor neurons carrying the FUS mutation [90]. Similarly, global histone hypoacetylation was observed in a FUS murine model. The restoration of histone acetylation levels in these mice by HDAC inhibition ameliorated the disease phenotype and significantly extended their lifespan [91]. In addition, HDAC6 inhibition restored axonal transport defects and mitochondrial and endoplasmic reticulum vesicle transport defects in ALS patient-derived motor neurons by increasing the α-tubulin acetylation level [92,93].

In HD rats and mouse models, HDAC inhibition produces a variety of neuroprotective beneficial effects, including partial reversal of behavioral symptoms, reversion of aberrant neuronal differentiation [94], prevention of striatal neuronal atrophy, improvement of motor performance [95], amelioration of disease phenotypes in a transgenerational manner [96] and reestablishment of pyruvate dehydrogenase activity improving mitochondrial function and bioenergetics [97]. Moreover, a multiomic study has proposed that the positive effect of HDAC4 knockdown in rescuing synaptic function in HD mice could be a consequence of synaptic vesicle trafficking regulation, and HDAC4 could interact with htt via association with htt-interacting proteins [98]. Other HDACs have also been proposed as therapeutic targets in HD. Striatal HDAC2 levels are reduced in the YAC128 HD mouse model subjected to dietary restriction, which could contribute to improving the disease phenotype [99]. In addition, inhibition of HDAC3 improves motor deficits, suppresses striatal CAG repeat expansions, and reduces the accumulation of oligomeric forms of mutant htt in HD transgenic mice [100,101]. In contrast, genetic deletion of HDAC6 exacerbates social impairments and hypolocomotion in HD R6/1 mice [102].

Although there are fewer works analyzing this epigenetic mechanism compared to DNA methylation or microRNAs, the results obtained seem to be promising, not as a source of biomarkers but as a possible target for therapies.

Other histone modifications have been studied, but the number of these studies is even lower. A genome-wide study in human brains has identified differential enrichment of trimethylated lysine 4 of histone 3 (H3K4me3) mark between HD and control samples [103]. Interestingly, in a Drosophila melanogaster HD model, the activity reduction of the H3K27-specific demethylase, Utx, ameliorated neurodegeneration and diminished htt aggrega-
tion [104]. Conversely, in this same model, histone methyltransferase dSETDB1/ESET was identified as a mediator of mutant htt-induced degeneration [105].

### Table 2. Histone post-translational modifications in prion-like diseases.

| Disease                  | Species/Model | Tissue Type       | Main Finding                                                                 | References |
|--------------------------|---------------|-------------------|-------------------------------------------------------------------------------|------------|
| Alzheimer’s disease      | Human         | Brain             | Widespread acetylomic variation associated with AD, possibly induced by pathological tau | [69,70]    |
|                          | Human         | Frontal cortex, hippocampus | Decreased levels of HDAC1                                                   | [73]       |
|                          | Human         | Frontal cortex    | Decreased levels of HDAC2 contributing to neuronal dysfunction, neurofibrillary tangles pathology, and cognitive decline | [73,74]    |
|                          | 3xTg-AD mice, Human | Human iPS-derived neurons | HDAC3 inhibition decreases pathological tau phosphorylation and acetylation | [75]       |
|                          | ADLP−APT mice, Human | Human-derived brain organoids | HDAC6 inhibition stimulates pathological tau degradation                     | [77]       |
|                          | Human         | Dopaminergic neurons | PD neurotoxins increase histone acetylation through an autophagy-mediated HDACs reduction mechanism | [71]       |
|                          | Human         | Fibroblasts       | Imbalance between total HATs and HDACs activities                            | [72]       |
|                          | LRRK2 R1441G mice | Brain            | HDAC inhibition has a neuroprotective effect through modulation of neuroinflammation and improvement of PD-like behaviors | [79]       |
|                          | Sirt2−/− C57- BL6 mice, Human | Brain | Sirtuin-2 deacetylase inhibition protects degenerating dopaminergic neurons, reduces microglial activation, and facilitates the trafficking and clearance of misfolded proteins | [80,81]    |
|                          | Human         | Microglia from the substantia nigra | Upregulation of HDAC2                                                         | [83]       |
|                          | E13-14 mice   | Dopaminergic neurons | HDAC4 accumulation promotes neuronal apoptosis                                | [84]       |
|                          | C57-BL6 mice  | Brain             | HDAC6 could contribute to oxidative injury                                    | [86]       |
|                          | SOD1−ALS mice | Skeletal muscle   | Increase in class II HDACs (4, 5, and 6) involved in modulating the expression and function of glutamate transporter | [85,86]    |
|                          | Human         | iPSC-derived motor neurons | HDAC inhibition rescues the DNA repair response                               | [90]       |
|                          | Tg FUS +/+ mice | Spinal cord       | Global histone hypoacetylation. Restoration of histone acetylation ameliorates the disease phenotype | [91]       |
|                          | Human         | iPSC-derived motor neurons | HDAC6 inhibition restores axonal transport defects and mitochondrial and endoplasmic reticulum vesicle transport defects | [92,93]    |
|                          | Human         | Brain             | No significant differences in HDAC expression levels between patients and controls | [97]       |
|                          | SOD1−ALS mice | Human             | Decreased expression of HDAC4 associated with an earlier onset of the disease | [87,88]    |
|                          | tgHD rats, BACHD, R6/2, YAC128 mice | Brain | HDAC inhibition produces neuroprotective beneficial effects                  | [94–97]    |
|                          | HttQ20, HttQ140 mice | Brain | HDAC4 regulates synaptic vesicle trafficking and interacts with htt          | [98]       |
|                          | YAC128 mice   | Brain             | Reduction of HDAC2 could contribute to improving the disease phenotype        | [99]       |
|                          | N171-82Q, HdhQ111 knock-in mice | Brain | HDAC3 inhibition improves motor deficits, suppresses striatal CAG repeat expansions, and reduces accumulation of mutant huntingtin oligomeric forms | [100,101] |
|                          | R6/1 mice     | In vivo assessment | HDAC6 deletion exacerbates social impairments and hypolocomotion              | [102]      |
|                          | Human         | Brain             | Differentially enrichment of H3K4me3 mark                                    | [103]      |
|                          | Drosophila melanogaster | Brain, eye | Activity reduction of Utx ameliorates neurodegeneration and diminishes htt aggregation. dSETDB1/ESET might be a mediator of mutant htt-induced degeneration | [104,105] |

### 2.3. MicroRNAs

A large number of human proteins containing prion-like domains are RNA or DNA-binding proteins [106]. The first protein with these motifs associated with neurodegeneration was TDP-43 (trans-activation response element DNA-binding protein 43) [107,108], which is the major pathological protein in sporadic ALS. This protein plays a role in many RNA-related functions, including microRNA biogenesis. Afterward, many other proteins related to neurodegenerative diseases have been discovered that play a role in...
RNA metabolism, and amyloids coaggregate with endogenous nucleic acids [109,110]. Although different RNA species may be altered in prion-like diseases, we focus on the role of microRNA in these pathologies. These biomolecules have been widely studied in neurodegenerative diseases. Changes in miRNA expression profiles may serve as biomarkers, and these molecules seem to play important roles in the neuropathology of these diseases.

2.3.1. MicroRNA Profiles

Several studies have measured miRNA expression profiles in tissues and body fluids from patients and in different in vitro and animal models of prion-like diseases. Sets of microRNAs altered in each prion-like disease seem to be largely different, as summarized in Table 3.

In AD patients, miRNA profiles have been analyzed in brain [111–114], blood [115,116], serum [117,118], CSF [119] and extracellular vesicles (EVs) [120–122]. Brain and EVs miRNA profiles have as well been characterized in AD mouse models [123–125]. Comparing the different profiles, only one miRNA, miR-324-3p, is commonly downregulated in the brain, body fluids, and EVs of AD patients, but its expression is not altered in AD mouse models. MiRNA profiles have been also characterized in brain [126–129], gut [130], blood [128], plasma [131,132], serum [133], CSF [134,135], saliva [136], and EVs [131,137] of PD patients; in brain of a PD mouse model [135]; in blood of a PD rat model [138]; and in a PD in vitro model [139]. Although no common miRNAs are found when comparing all the above-mentioned PD profiles, there are common miRNAs between some tissues and body fluids. MicroRNA miR-451a is upregulated in the brain, gut, and CSF of PD patients and also in the brains of PD mice, and miR-19b-3p is downregulated in the brain, blood, plasma, and saliva of PD patients.

In ALS patients, microRNAs have been studied in brain [140,141], skeletal muscle [142,143], blood [143–146], plasma [147], serum [148–150], CSF [151] and EVs [152–155]. Distinctive ALS miRNA profiles are also present in mouse skeletal muscle [156] and serum [157] and in in vitro models [154,155]. Three miRNAs, miR-125a-3p, miR-193a-5p, and miR-455-3p, are commonly downregulated in the brain, skeletal muscle, blood, and serum from ALS patients, and the expression of miR-125a-5p, which is downregulated in the brain and skeletal muscle of ALS patients, is also reduced in ALS mouse models and in vitro models. A smaller number of studies have explored the miRNA profiles in HD. These profiles are found in the brain [159–161], plasma [162], and CSF [163] of HD patients and in the brain of HD mouse models [164–167]. No common miRNAs are found between the profiles performed in HD patients, but there are two miRNAs, miR-10b-5p and miR-10a-5p, that are upregulated in the brain of both HD patients and mouse models.

When comparing the human miRNA profiles of the four prion-like diseases, there are two miRNAs, miR-144-3p and miR-22-5p, that appear upregulated in all four pathologies (Figure 2a). The β-amyloid precursor protein (APP) has been identified as a target gene of miR-144-3p, which seems to have a role in mitochondrial function maintenance [168], and a potential neuroprotective role has been predicted for miR-22 related to the regulation of targets implicated in HD such as HDAC4 [169]. Further analyses are necessary to verify if these two microRNAs display important roles in misfolded protein-related diseases.

Conversely, although there are miRNAs similarly downregulated between two or three prion-like diseases, no common downregulated miRNAs are found between the four diseases (Figure 2b). The existence of differently regulated microRNA in different diseases can be used as a source of biomarkers for differential diagnosis. Supplementary Table S2 lists common upregulated and downregulated miRNAs for combinations of different prion-like diseases and the datasets used to generate the Venn diagrams.
2.3.2. The Role of microRNAs in Prion-Like Diseases

In addition to miRNA profiles that could reveal potential disease biomarkers, some studies have shed light on the functions or possible roles of different miRNAs in prion-like diseases. In AD pathology, several miRNAs seem to have neuroprotective roles attenuating Aβ accumulation and its associated neurotoxicity. In particular, the following miRNAs have been associated with this neuroprotective function: miR-193a-3p [170] and miR-133b [171] in human serum, miR-335-5p [172] and miR-361-3p [173] in the human brain, miR-200a-3p [174] in plasma from AD patients, miR-107 [175] in human neuroblast cell lines, and miR-340 [176] in the hippocampus from senescence-accelerated (SAMP8) mice that show increased oxidative damage associated with APP overproduction. Moreover, in rat hippocampus, miR-134-5p [177] is involved in rescuing AD synaptic plasticity deficit, and miR-124 [178] and miR-200a-3p [174] are involved in alleviating tau pathology in murine and in vitro models, respectively. On the other hand, miR-34c [179] and miR-124 [180]...
mediate synaptic and memory deficits in AD. Other miRNAs recently described to likely participate in AD risk and progression are miR-146a, miR-181a, detected in blood from AD patients, and miR-142-3p [181,182] in the human brain. All aforementioned miRNAs have been proposed as potential diagnostic biomarkers and/or therapeutic targets for AD pathology.

Dysregulation of miRNAs is also implicated in PD pathogenesis. The upregulation of several miRNAs, including miR-150 [183] in human serum, miR-let-7a [184], and miR -190 [185] in C57BL/6 mouse model and miR-135b [186] in vitro models, ameliorates PD-associated neuroinflammation. By inhibiting SP1, a transcription factor expressed in the brain, miR-375 decreases dopaminergic neurons' damage, reduces oxidative stress, and diminishes inflammation in PD, and miR-29c also attenuates dopaminergic neuron loss, neuroinflammatory response, and α-synuclein accumulation [187,188]. Furthermore, in a PD rat model, miR-3557 and miR-324 seem to be involved in delaying PD neurodegeneration [189], and overexpression of miR-410 in a PD cellular model appears to exert neuroprotective effects against apoptosis and reactive oxygen species production [190]. In contrast, overexpression of miR-326 has been described to promote autophagy of dopaminergic neurons, and miR-195 downregulation might induce microglia-mediated neuroinflammation activation [191,192]. On the other hand, miR-7 seems to be involved in regulating BDNF expression in the early stages of PD, and miR-376a could also be implicated in PD pathogenesis, possibly by regulating the expression of mitochondrial-related genes [193,194].

Several studies also report miRNA changes in ALS, suggesting that these molecules could play a role in the development and progression of the disease. In serum from ALS patients, downregulation of miR-335-5p may enhance mitophagy, autophagy, and apoptosis pathways [195]. Interestingly, in the spinal cord of an ALS mouse model, downregulated miR-375-3p appears to control various target structures that intervene at different sites of the apoptosis pathway [196]. In contrast, in the cerebellum of an ALS mouse model, increased miR-29b-3p seems to downregulate proapoptotic factors, leading to neuroprotection [197]. Regarding to axon degeneration, several miRNAs, namely miR-126-5p [198], miR-494 -3p [199] and miR-1825 [200], might facilitate this pathological feature in ALS. On the other hand, upregulated miR-338-3p is responsible for decreased glycogenolysis and subsequent glycogen accumulation within the spinal cord of SOD1-ALS mice [201], and miR-105 and miR-9 seem to potentially contribute to the pathogenesis of intermediate filament inclusions in ALS [202]. Furthermore, it has been described that extracellular miR-218 released from dying motor neurons in ALS can be taken up by neighboring astrocytes and negatively affect astrocyte function [203]. In the skeletal muscle of FALS patients, it has been reported an upregulation of miR-206, involved in the neuromuscular junction, regeneration, and muscle atrophy, and also an increase in inflammatory miRNAs (miR-27a, miR-221, miR-155) [79]. miR-206, a microRNA that was consistently altered during the course of the disease in the skeletal muscle of the SOD1-G93A ALS mouse model, is also increased in serum from ALS patients [155]. Mechanistically, it has been suggested that increased miR-206 is an attempt to promote maintenance and/or repair of neuromuscular junctions by targeting and inhibiting HDAC4, which leads to a fibroblast growth factor (FGF)-stimulated reinnervation [204]. Finally, reduced expression of the miR-17~92 cluster has been associated with the vulnerability of limb-innervating lateral motor column motor neurons to ALS-related degeneration [205].

In HD, a consistent association between expression profiles of CSF-miRNAs and the earliest prodromal stages of the disease has been reported [162]. In contrast, a study in a knock-in mouse model of HD (Hdh mice) suggests that miRNA regulation may have a limited global role in responding to HD in the striatum and cortex of these mice [206]. A decrease in miR-132 has been observed in the brain of another model of HD (HD R6/2 mice), and restoration of miR-132 deficiency seems to confer amelioration in motor function and lifespan of these mice [207]. In neural progenitors and differentiated neural cells of a transgenic HD nonhuman primate model and in HD murine primary neurons, miR-196a has shown neuroprotective effects, including improvement of cell survival and
mitochondrial functions, reduction of cytotoxicity and apoptosis and enhancement of neuronal morphology and differentiation \cite{208,209}. Regarding htt, miR-27a has been reported to reduce mutant htt aggregation in R6/2-derived neuronal stem cells \cite{210}. Interestingly, artificial miRNAs have also been used to successfully reduce mutant htt levels in a transgenic HD sheep model and in a humanized Hu128/21 HD mouse model \cite{211,212}.

As reported, the role of microRNAs in these neurodegenerative diseases is better known than the ones of the other epigenetic mechanisms. We have the tools to analyze the effect of overexpressing or repressing the expression of these molecules using expression vectors or antisense oligonucleotides in cellular models. This could facilitate the research in therapies modifying dysregulated microRNAs.

Table 3. MicroRNAs in prion-like diseases.

| Disease               | Species/Model         | Tissue Type                                                                 | miRNA                                                                 | Main Finding                                                                                           | References |
|-----------------------|-----------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|------------|
| Alzheimer’s disease   | Human                 | Brain, peripheral blood, serum, CSF, serum and CSF exosomes, and plasma extracellular vesicles | miRNA profiles                                                      | Differential miRNA expression profiles in AD patients                                                  | [111–122] |
|                       | APP/PS1 and 5XFAD mice| Brain and urinary exosomes                                                | miRNA profiles                                                      | Differential miRNA expression profiles in AD mouse models                                              | [123–125] |
|                       | Human                 | Serum                                                                      | miR-193a-3p, miR-133b                                               | Neuroprotective roles attenuating Aβ accumulation and its associated neurotoxicity                    | [170,171] |
|                       | Human                 | Brain                                                                      | miR-335-5p, miR-361-3p                                              | Associated with AD risk and progression                                                              | [172,173] |
|                       | SAMP8 mice            | Hippocampus                                                                | miR-340                                                            | Alleviates tau pathology and mediates synaptic and memory deficits                                   | [174]      |
|                       | Human                 | SH-SY5Y, SK-N-SH cells                                                    | miR-107                                                            | Amelioration of PD-associated neuroinflammation                                                     | [175]      |
|                       | Human                 | Blood plasma                                                               | miR-200a-3p                                                        | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [176]      |
|                       | Rat                   | Hippocampus                                                                | miR-134-5p                                                        | Amelioration of PD-associated neuroinflammation                                                     | [177]      |
|                       | C57BL/6J, Tg2576 mice | Hippocampus                                                                | miR-124                                                           | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [178,180] |
|                       | SAMP8 mice, Human     | Hippocampus, serum                                                         | miR-34c                                                           | Amelioration of PD-associated neuroinflammation                                                     | [179]      |
|                       | Human                 | Blood, Brain                                                               | miR-146a, miR-181a, miR-142-3p                                    | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [180]      |
| Parkinson’s disease   | Human                 | Brain, gut, plasma, serum, CSF, saliva, plasma exosomes, and iPSC-derived dopaminergic neurons | miRNA profiles                                                      | Differential miRNA expression profiles in PD patients                                               | [126–137] |
|                       | Rat                   | Peripheral blood                                                           | miRNA profile                                                      | Differential miRNA expression profile in a PD rat model                                               | [138]      |
|                       | Human                 | Serum                                                                      | miR-150                                                           | Amelioration of PD-associated neuroinflammation                                                     | [139]      |
|                       | C57BL/6 mice          | Brain                                                                      | miR-let-7a, miR-190                                                | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [181,182] |
|                       | Human, rat            | SH-SY5Y, PC-12 cells                                                       | miR-135b                                                          | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [183]      |
|                       | Wistar rats, C57BL/6 mice, Human | Brain, SH-SY5Y cells                                                      | miR-375, miR-29c                                                    | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [184,185] |
|                       | Sprague-Dawley rats   | Brain                                                                      | miR-3557, miR-324                                                  | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [186]      |
|                       | Human, rat            | SH-SY5Y, PC-12 cells                                                       | miR-410                                                           | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [187,188] |
|                       | C57BL/6 mice          | Brain                                                                      | miR-326                                                           | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [189]      |
|                       | Mouse                 | BV2 cells                                                                  | miR-195                                                           | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [190]      |
|                       | Sprague-Dawley rats   | Peripheral blood, brain                                                   | miR-7                                                              | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [191]      |
|                       | Human                 | PBMCs, SH-SY5Y cells                                                       | miR-376a                                                          | Decrease in dopaminergic neurons’ damage and neuroinflammatory response                             | [192]      |
### Table 3. Cont.

| Disease               | Species/Model          | Tissue Type                                                                 | miRNA                                      | Main Finding                                                                                                               | References |
|-----------------------|------------------------|----------------------------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------|
| Amyotrophic lateral sclerosis | Human                  | Brain, spinal cord, skeletal muscle, neuromuscular junctions, plasma, serum, leukocytes, CSF, plasma, serum, brain and spinal cord extracellular vesicles, motor neuron-derived exosomes, iPSC-derived motor neurons, and motor neuron progenitors | miRNA profiles | Differential miRNA expression profiles in ALS patients | [140–155] |
|                       | SOD1<sup>G93A</sup> and SOD1<sup>G86R</sup> mice | Serum, skeletal muscle                                                                 | miRNA profiles | Differential miRNA expression profiles in ALS mouse models | [156,157] |
| Human                 | Serum                  | miR-335-5p                                                                  | Downregulation may enhance mitophagy, autophagy, and apoptosis pathways | [195] |
| Wobbler mice          | Spinal cord            | miR-375-3p                                                                  | Regulates target structures that intervene at the apoptosis pathway | [196] |
| Wobbler mice          | Cerebellum             | miR-29b-3p                                                                  | Downregulates proapoptotic factors, leading to neuroprotection | [197] |
| SOD1<sup>G93A</sup> mice | Muscle                | miR-126-5p                                                                  | Involved in axon degeneration | [198] |
| Human                 | Astrocytes             | miR-494-3p                                                                  | Upregulation decreases glycogenolysis causing glycogen accumulation within the spinal cord | [201] |
| Human, SOD1<sup>G93A</sup> mice | Skeletal muscle, serum, plasma | miR-206                                                                    | Upregulated. Involved in neuromuscular junction, regeneration, and muscle atrophy | [79,156] |
| Human, SOD1<sup>G93A</sup> mice | Skeletal muscle | miR-27a, miR-221, miR-155 | Increased in FALS patients | [79] |
| Human, SOD1<sup>G93A</sup> mice | Motor neurons | miR-17–92 cluster       | Associated with vulnerability of motor neurons to ALS-related degeneration | [205] |
| C57BL/6, R6/1 and BACHD mice | Brain          | miRNA profiles | Differential miRNA expression profiles in HD mouse models | [164–167] |
| Human                 | Brain, plasma, CSF     | miRNA profiles | Differential miRNA expression profiles in HD patients. Association between CSF-miRNAs expression profiles and the earliest prodromal stages of HD | [172–176] |
| Hdh mice              | Striatum, cortex       | miRNA profiles | miRNA regulation may have a limited global role in responding to HD | [206] |
| R6/2 mice             | Brain                  | miR-132                                                                    | Decreased levels, whose restoration confers amelioration in motor function and lifespan | [207] |
| FVB mouse embryos, HDI/HDI/WT monkey | Neural progenitors, neural cells | miR-196a | Neuroprotective effects | [208,209] |
| R6/2 mice             | Neuronal stem cells    | miR-27a                                                                    | Reduces mutant htt aggregation | [210] |
| Hui128/21 mice, sheep | Striatum               | Artificial miRNAs             | Reduce mutant htt levels | [211,212] |

### 3. Epigenetic Changes in Prion Diseases

Compared to prion-like diseases, there are very few studies on the involvement of epigenetic changes in transmissible spongiform encephalopathies.

It is known that the prion protein (PrP) is able to bind to RNA and DNA molecules [213]. As these nucleic acids can induce PrP aggregation, they have been proposed as catalysts in the conversion of the PrP<sup>C</sup> to the pathologic form PrP<sup>Sc</sup> [214]. Different DNA molecules are capable of binding to recombinant PrP (rPrP), resulting in complex aggregates [215]. Interestingly, the GC content of these DNA molecules seems to be important in the binding, affinity, stability, and aggregation abilities and in the toxic species generation [215]. A recent
study has evaluated the neurotoxic effect of the inoculation of a PrP-DNA complex in the lateral ventricle of Swiss mice, which, after inoculation, showed cognitive impairment, hippocampal synapse loss, and intense glial activation [216]. In contrast, in human neuroblastoma cell cultures, PrP cytotoxicity is attenuated when combined with DNA molecules, which stabilize PrP structure and reduce its pathogenic properties [217].

Different RNA molecules can also bind to PrP and trigger its aggregation and conversion to PrPSc, the efficiency of the conversion depending on the RNA source [216,218,219]. Some of these RNA molecules, specifically RNA aptamers, are able to bind and stabilize PrPC and reduce PrPSc levels in infected mouse neuronal cells [220]. Further studies are needed in order to evaluate the involvement of these nucleic acids in prion pathology and to develop potential therapeutic strategies.

3.1. DNA Methylation Profiles

DNA methylation might also be involved in the pathogenesis of prion diseases. A study of the mouse prion protein gene (PRNP) encoding the PrPC protein has reported an association between DNA methylation and PRNP gene expression. The PRNP gene promoter region seems to be unmethylated, and the methylation status of one of the PRNP enhancer regions was negatively correlated with PRNP expression [221]. In addition, during neuronal differentiation of mouse embryonic carcinoma P19C6 cells, the expression of PRNP was markedly increased, while CpG methylation was significantly reduced, suggesting that DNA methylation could be implicated in mediating PRNP expression regulation [222].

Only three studies have analyzed the methylome of prion diseases. A genome-wide methylation study has shown differentially methylated positions in blood from sporadic Creutzfeldt–Jakob disease (sCJD) patients compared with healthy controls, some of these positions correlated with disease progression [223]. Furthermore, another genome-wide methylation study of the CNS of sheep naturally infected with scrapie has identified differentially methylated regions between control and scrapie animals, belonging some of them to genes with possible neuroprotective roles and to genes that may contribute to scrapie disease progression [224]. Interestingly, a recent study was able to identify different DNA methylation patterns in tonsil and appendix lymphoreticular tissues between sCJD patients and healthy individuals [225], pointing to a potential source of diagnostic biomarkers in prion diseases.

Although these three works have been performed in different tissues (blood, CNS, and lymphoid tissues) and species (CJD human patients and scrapie-infected sheep) and have used different methodologies (450k methylation array for humans and whole genome bisulfite sequencing), we have compared the genes detected in each work containing either DMR or DMP. Twelve genes were differentially methylated in both ovine CNS and CJD blood. Further studies are necessary to confirm the role of these common genes in prion diseases. Supplementary Table S4 shows the common DMR and DMP in prion and prion-like diseases.

We have compared the methylation DMR and DMP profiles between these studies and those performed in prion-like diseases. As different methodology has been used, only DMPs obtained in CJD samples were compared with the other diseases. Only 2 DMPs identified in CJD blood were found in common with AD, 3 with PD, and 1 with ALS. However, of a total of 8907 DMRs observed in CNS of scrapie-infected sheep, 634 are also altered in PD, 60 in Alzheimer’s, 51 in ALS, and 61 in HD. This large difference is due to the fact that PD and scrapie were analyzed using the same methodology, bisulfite-treated DNA sequencing. More such studies are needed in the other prion-like diseases to determine whether or not there are common genes differentially methylated in all prion-misfolded pathologies.

3.2. Histone Modifications

Yeast ESI+, for expressed sub-telomeric information, is the prion form of the Set3C histone deacetylase scaffold Snt1 (NCOR1 in humans). This prion, in response to cell cycle
arrest, is able to activate gene expression through H4 acetylation and RNA polymerase II recruitment [226]. Other histone deacetylases, namely HDAC6 and sirtuin-1 (SIRT1), have shown protective effects during prion infection. Although many studies in prion-like diseases are addressed to inhibit HDAC6 as a potential therapeutic approach, in cerebral cortical neurons, overexpression of HDAC6 alleviates prion peptide-mediated neuronal cell death and toxicity [227]. On the other hand, overexpression of SIRT1, which is decreased in the brains of scrapie-infected rodents and in prion-infected SMB-S15 cells, reduces PrPSc levels and protects against prion protein-induced neuronal cell death and mitochondrial dysfunction [228–230]. Therefore, although HDAC inhibition is proposed as a potential therapeutic strategy in prion-like diseases, this approach does not seem the best choice for treating prion diseases. Further analysis will be necessary to find out the role of other HDACs in prion diseases and to design novel therapies that maybe could be focused on the overexpression of HDACs.

3.3. MicroRNA Profiles

A number of studies have reported changes in miRNA expression profiles during prion infection in the CNS, plasma, and synaptoneurosomes of preclinical and clinical scrapie-infected mice [231–233], in the serum of elk infected with the chronic wasting disease (CWD) [234] and in plasma of naturally infected classical scrapie sheep [235]. When comparing these profiles with the ones reported in prion-like diseases, there are some miRNAs commonly altered in the two groups of diseases. Table 4 shows the common upregulated, and downregulated miRNAs, and Supplementary Table S3 lists the datasets generated from the different miRNA profile studies in prion diseases. The prion-like disease with more miRNAs in common with prion diseases is ALS, whereas the one with fewer miRNAs in common is HD. More studies are required in order to find specific miRNAs that are only altered in prion diseases, even only in each type of prion disease, specifically for their use as diagnostic biomarkers.

| miRNA            | Prion Diseases | AD | PD | ALS | HD | Upregulated (+)/Downregulated (−) |
|------------------|----------------|----|----|-----|----|----------------------------------|
| miR-5100         | +             | +  | +  | +   |    | Upregulated                      |
| miR-342-3p       | +/−           | −  | +/−| +/− |    | Upregulated/Downregulated       |
| let-7f-5p        | +            | +  | +  |    |    | Upregulated                      |
| miR-146b-5p      | +            | +  | +  |    |    | Upregulated                      |
| let-7a-5p        | +            | +  | +  |    |    | Upregulated                      |
| miR-378c         | +            | +  | +  |    |    | Upregulated                      |
| miR-27a-3p       | +            | +  | +  |    |    | Upregulated                      |
| miR-339-3p       | +            | +  | +  |    |    | Upregulated                      |
| miR-142-5p       | +            | +  | +  |    |    | Upregulated                      |
| miR-146a-5p      | +            |    | +  |    |    | Upregulated                      |
| miR-320a-3p      | +/−           | −  | +  | +/− |    | Upregulated/Downregulated       |
| miR-10a-5p       | +            | +  | +  |    |    | Upregulated                      |
| miR-326          | +            |    | +  |    |    | Upregulated                      |
| miR-21-5p        | +            | +  | +  |    |    | Upregulated                      |
| miR-324-5p       | +            | +  | +  |    |    | Upregulated                      |
| miR-103a-3p      | +            | +  | +  |    |    | Upregulated                      |
| miR-331-3p       | +/−           | −  | +  | +/− |    | Upregulated/Downregulated       |
| miR-107          | +            |    | +  |    |    | Upregulated                      |
| miR-142-3p       | +            |    | +  |    |    | Upregulated                      |
| miR-129-5p       | −            | −  | −  | −   |    | Downregulated                    |
| miR-423-5p       | −            | −  | −  | −   |    | Downregulated                    |
| miR-125a-5p      | −            | −  | −  | −   |    | Downregulated                    |
| miR-148a-3p      | −            | −  | −  | −   |    | Downregulated                    |
Although the potential role of most of these alterations in TSE pathology is unknown, multiple miRNAs regulate PrP\textsuperscript{C} levels both directly and indirectly in human neuroectodermal cell lines [236]. On the other hand, miR-16, which is increased in hippocampal neurons during presymptomatic prion disease, could decrease neurite length and branching, probably via the downregulation of components of the MAPK/ERK pathway [237]. Additionally, a single nucleotide polymorphism in miR-146a has been associated with susceptibility to FFI (fatal familial insomnia) and with the appearance of some clinical features in sCJD patients [238]. Interestingly, artificial miRNAs have also been used to reduce PrP\textsuperscript{C} and subsequently suppress PrP\textsuperscript{Sc} propagation in primary mixed neuronal and glial cells culture [239].

4. Concluding Remarks

It is evident that epigenetic mechanisms, namely DNA methylation, histone post-translational modifications, and microRNAs, are involved in the pathophysiology of neurodegenerative diseases. Increasing evidence in prion-like diseases and, more recently, in prion diseases has shown that epigenetic modifications can modulate different pathogenic mechanisms occurring in these neurodegenerative disorders. Nevertheless, these epigenetic mechanisms seem to act differently in each of these diseases. Global DNA methylation changes have been detected in prion diseases and prion-like diseases in a variety of tissues and in several specific genes, showing different trends in the global methylation profile of each disease and several genes harboring differentially methylated regions and positions.
that match between some of these diseases. Modulation of HDAC enzymes seems to also be a common epigenetic mechanism in these diseases. Interestingly, among all the HDACs, the enzyme HDAC6 is involved in both prion diseases and prion-like diseases, although the mechanism of action is different between the two groups of diseases. On the other hand, other HDACs, namely HDAC2, HDAC3, and HDAC4, are associated with different aspects of prion-like diseases. Additionally, miRNA profiles seem to be the most specific of each disease. However, there are two miRNAs, miR-144-3p and miR-22-5p, that seem to be commonly upregulated in the four prion-like diseases but not in prion diseases, and other miRNAs, such as miR-335-5p, miR-375, and miR-27a, have functions in AD, PD, HD, and ALS, but they seem to regulate different pathways in each disease. Prion and prion-like diseases also share several miRNAs in common, ALS being the prion-like disease with the highest number of common miRNAs. In addition, artificial miRNAs have successfully been used in both HD and prion diseases to reduce misfolded protein levels. Further research is still needed, especially in prion diseases where knowledge is still scarce, in order to elucidate the exact molecular pathways by which these epigenetic mechanisms perform their regulatory roles and to identify potential epigenetic diagnostic and therapeutic biomarkers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms232012609/s1. References [19–37,111–122,126–137,140–155,159–163,231–235] are cited in the Supplementary Materials.

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References
1. Moore, L.D.; Le, T.; Fan, G. DNA Methylation and Its Basic Function. Neuropsychopharmacology 2013, 38, 23–38. [CrossRef] [PubMed]
2. Audia, J.E.; Campbell, R.M. Histone Modifications and Cancer. Cold Spring Harb. Perspect. Biol. 2016, 8, a019521. [CrossRef] [PubMed]
3. Zhang, J.; Jing, L.; Li, M.; He, L.; Guo, Z. Regulation of histone arginine methylation/demethylation by methylase and demethylase (Review). Mol. Med. Rep. 2019, 19, 3963–3971. [CrossRef] [PubMed]
4. Huang, W. MicroRNAs: Biomarkers, diagnostics, and therapeutics. Methods Mol. Biol. 2017, 1617, 57–67.
5. Place, R.F.; Li, L.C.; Pookot, D.; Noonan, E.J.; Dahiya, R. MicroRNA-373 induces expression of genes with complementary promoter sequences. Proc. Natl. Acad. Sci. USA 2008, 105, 1608–1613. [CrossRef]
6. Bottani, M.; Banfi, G.; Lombardi, G. Perspectives on miRNAs as Epigenetic Markers in Osteoporosis and Bone Fracture Risk: A Step Forward in Personalized Diagnosis. Front. Genet. 2019, 10, 1044. [CrossRef]
7. Lardenoije, R.; Iatrou, A.; Kenis, G.; Kompotis, K.; Steinbusch, H.W.; Mastroeni, D.; Coleman, P.; Lemere, C.A.; Hof, P.R.; van den Hove, D.L.A.; et al. The epigenetics of aging and neurodegeneration. Prog. Neurobiol. 2015, 131, 21–64. [CrossRef]
8. Hwang, J.Y.; Aromolaran, K.A.; Zukin, R.S. The emerging field of epigenetics in neurodegeneration and neuroprotection. Nat. Rev. Neurosci. 2017, 18, 347–361. [CrossRef]
9. Heyward, F.D.; Sweatt, J.D. DNA Methylation in Memory Formation: Emerging Insights. Neuroscientist 2015, 21, 475–489. [CrossRef]
10. Miller, C.A.; Sweatt, J.D. Covalent Modification of DNA Regulates Memory Formation. Neuron 2007, 53, 857–869. [CrossRef]
11. Hu, Z.; Li, Z. miRNAs in synapse development and synaptic plasticity. Curr. Opin. Neurobiol. 2017, 45, 24–31. [CrossRef] [PubMed]
12. Goldemichael, B.T.; Mansuy, I.M. Micro-RNAs in cognition and cognitive disorders: Potential for novel biomarkers and therapeutics. Biochem. Pharmacol. 2016, 104, 1–7. [CrossRef] [PubMed]
13. Aksoy-Aksel, A.; Zampa, F.; Schratt, G. MicroRNAs and synaptic plasticity—a mutual relationship. Philos. Trans. R. Soc. B Biol. Sci. 2014, 369, 20130515. [CrossRef]
14. Jaunmuktane, Z.; Brandner, S. Invited Review: The role of prion-like mechanisms in neurodegenerative diseases. *Neuropathol. Appl. Neurobiol.* 2019, 46, 522–545. [CrossRef]

15. Masnata, M.; Sciaccia, G.; Maxan, A.; Bousset, L.; Denis, H.L.; Lauruol, F.; David, L.; Saint-Pierre, M.; Kordower, J.H.; Melki, R.; et al. Demonstration of prion-like properties of mutant huntingtin fibrils in both in vitro and in vivo paradigms. *Acta Neuropathol.* 2019, 137, 981–1001. [CrossRef] [PubMed]

16. Ma, J.; Wang, F. Prion disease and the ‘protein-only hypothesis’. *Essays Biochem.* 2014, 56, 181–191. [CrossRef]

17. Prusiner, S. Novel proteinaceous infectious particles cause scrapie. *Science* 1982, 216, 136–144. [CrossRef]

18. Chakravarty, A.K.; Jarosz, D.F. More than Just a Phase: Prions at the Crossroads of Epigenetic Inheritance and Evolutionary Change. *J. Mol. Biol.* 2018, 430, 4607–4618. [CrossRef]

19. Li, H.; Guo, Z.; Guo, Y.; Li, M.; Yan, H.; Cheng, J.; Wang, C.; Hong, G. Common DNA methylation alterations of Alzheimer’s disease and aging in peripheral whole blood. *Oncotarget* 2016, 7, 19089–19098. [CrossRef]

20. Li, Q.S.; Vasanthakumar, A.; Davis, J.W.; Idler, K.B.; Nho, K.; Waring, J.F.; Saykin, A.J.; for the Alzheimer’s Disease Neuroimaging Initiative (ADNI). Association of peripheral blood DNA methylation level with Alzheimer’s disease progression. *Clin. Epigenetics* 2021, 13, 191. [CrossRef]

21. Wang, C.; Chen, L.; Yang, Y.; Zhang, M.; Wong, G. Identification of potential blood biomarkers for Parkinson’s disease by gene expression and DNA methylation data integration analysis. *Clin. Epigenet.* 2019, 11, 24. [CrossRef] [PubMed]

22. Henderson, A.R.; Wang, Q.; Meechoovet, B.; Siniard, A.L.; Naymik, M.; de Both, M.; Huqentelman, M.J.; Caselli, R.J.; Driver-Dunkley, E.; Dunkley, T. DNA Methylation and Expression Profiles of Whole Blood in Parkinson’s Disease. *Front. Genet.* 2021, 12, 640266. [CrossRef] [PubMed]

23. Chuang, Y.-H.; Foul, K.C.; Bronstein, J.M.; Bordelon, Y.; Horvath, S.; Ritz, B. Parkinson’s disease is associated with DNA methylation levels in human blood and saliva. *Genome Med.* 2017, 9, 76. [CrossRef] [PubMed]

24. Hop, P.J.; Zwamborn, R.A.; Hannon, E.; Shireby, G.L.; Nabais, M.F.; Walker, E.M.; van Rheenen, W.; van Vught, J.J.; Dekker, A.M.; Westeneng, H.-J.; et al. Genome-wide study of DNA methylation shows alterations in metabolic, inflammatory, and cholesterol pathways in ALS. *Sci. Transl. Med.* 2022, 14, eabj0264. [CrossRef]

25. Zadel, M.; Mauer, A.; Kovanda, A.; Peterlin, B. DNA methylation profiles in whole blood of Huntington’s disease patients. *Front. Neurol.* 2018, 9, 655. [CrossRef]

26. Lu, A.T.; Narayan, P.; Grant, M.J.; Langfelder, P.; Wang, N.; Kwak, S.; Wilkinson, H.; Chen, R.Z.; Chen, J.; Bawden, C.S.; et al. DNA methylation study of Huntington’s disease and motor progression in patients and in animal models. *Nat. Commun.* 2020, 11, 4529. [CrossRef]

27. Zhao, J.; Zhu, Y.; Yang, J.; Li, L.; Wu, H.; de Jager, P.L.; Jin, P.; Bennett, D.A. A genome-wide profiling of brain DNA hydroxymethylation in Alzheimer’s disease. *Alzheimer’s Dement.* 2017, 13, 674–688. [CrossRef]

28. Watson, C.T.; Roussos, P.; Garg, P.; Ho, D.J.; Azam, N.; Katsel, P.; Haroutunian, V.; Sharp, A.J. Genome-wide DNA methylation profiling in the superior temporal gyrus reveals epigenetic signatures associated with Alzheimer’s disease. *Genome Med.* 2016, 8, 5. [CrossRef]

29. Gao, Z.; Fu, H.; Zhao, L.; Sun, Z.; Yang, Y.; Zhu, H. Aberrant DNA methylation associated with Alzheimer’s disease in the superior temporal gyrus. *Exp. Ther. Med.* 2017, 13, 103–108. [CrossRef]

30. Altuna, M.; Casado, A.U.; de Gordoa, J.S.-R.; Zelaya, M.V.; Labarga, A.; Lepesant, J.M.J.; Roldán, A.; Larumbe, R.; et al. DNA methylation signature of human hippocampus in Alzheimer’s disease is linked to neurogenesis. *Clin. Epigenetics* 2019, 11, 91. [CrossRef]

31. Smith, A.; Smith, R.G.; Pishva, E.; Hannon, E.; Rouboekos, J.A.Y.; Burrage, J.; Troakes, C.; Sloan, C.; Mill, J.; et al. Parallel profiling of DNA methylation and hydroxymethylation highlights neuropathology-associated epigenetic variation in Alzheimer’s disease. *Clin. Epigenetics* 2019, 11, 52. [CrossRef] [PubMed]

32. Young, J.I.; Sivasankaran, S.K.; Wang, L.; Ali, A.; Mehta, A.; Davis, D.A.; Dykxhoorn, D.M.; Petito, C.K.; Beecham, G.W.; Martin, E.R.; et al. Genome-wide brain DNA methylation analysis suggests epigenetic reprogramming in Parkinson disease. *Neurol. Genet.* 2019, 5, e342. [CrossRef] [PubMed]

33. Appleby-Mallinder, C.; Schaber, E.; Kirby, J.; Shaw, P.; Cooper-Knock, J.; Heath, P.R.; Highley, J.R. TDP43 proteinopathy is associated with aberrant DNA methylation in human amyotrophic lateral sclerosis. *Neuropathol. Appl. Neurobiol.* 2020, 46, 61–72. [CrossRef] [PubMed]

34. Wang, F.; Yang, Y.; Lin, X.; Wang, J.-Q.; Wu, Y.-S.; Xie, W.; Wang, D.; Zhu, S.; Liao, Y.-Q.; Sun, Q.; et al. Genome-wide loss of 5-hmc is a novel epigenetic feature of Huntington’s disease. *Hum. Mol. Genet.* 2013, 22, 3641–3653. [CrossRef]

35. Horvath, S.; Langfelder, P.; Kwak, S.; Aaronson, J.; Rosinski, J.; Vogt, T.E.; Eszes, M.; Foul, R.L.M.; Curtis, M.A.; Waldvogel, H.J.; et al. Huntington’s disease accelerates epigenetic aging of human brain and disrupts DNA methylation levels. *Aging* 2016, 8, 1485–1512. [CrossRef]

36. Fernández-Santiago, R.; Carballo-Carbajal, I.; Castellano, G.; Torrent, R.; Richaud, Y.; Sánchez-Danés, A.; Vilarasa-Blasi, R.; Sánchez-Pla, A.; Mosquera, J.L.; Soriano, J.; et al. Aberrant epigenome in iPSC-derived dopaminergic neurons from Parkinson’s disease patients. *EMBO Mol. Biol.* 2015, 7, 1529–1546. [CrossRef]

37. Fernández-Santiago, R.; Merkel, A.; Castellano, G.; Heath, S.; Raya, A.; Tolosa, E.; Martí, M.J.; Consiglio, A.; Ezquerra, M. Whole-genome DNA hyper-methylation in iPSC-derived dopaminergic neurons from Parkinson’s disease patients. *Clin. Epigenet.* 2019, 11, 108. [CrossRef]
38. Heberle, H.; Meirelles, G.V.; Da Silva, F.R.; Telles, G.P.; Minghim, R. InteractiVenn: A Web-Based Tool for the Analysis of Sets through Venn Diagrams. BMC Bioinform. 2015, 16, 169. [CrossRef]
39. De Souza, R.A.; Islam, S.A.; McEwen, L.M.; Mathelier, A.; Hill, A.; Mah, S.M.; Wasserman, W.W.; Kobor, M.S.; Leavitt, B.R. DNA methylation profiling in human Huntington’s disease brain. Hum. Mol. Genet. 2016, 25, 2013–2030. [CrossRef]
40. Horvath, S. DNA methylation age of human tissues and cell types. Genome Biol. 2013, 14, R115.
41. Li, P.; Marshall, L.; Oh, G.; Jakubowski, J.L.; Groot, D.; He, Y.; Wang, T.; Petronis, A.; Labrie, V. Epigenetic dysregulation of enhancers in neurons is associated with Alzheimer’s disease pathology and cognitive symptoms. Nat. Commun. 2019, 10, 2246. [CrossRef] [PubMed]
42. Sanchez-Mut, J.V.; Glauzer, L.; Monk, D.; Gräff, J. Comprehensive analysis of PM20D1 QTL in Alzheimer’s disease. Clin. Epigenet. 2020, 12, 20. [CrossRef] [PubMed]
43. Eryilmaz, I.E.; Cecener, G.; Eser, S.; Egeli, U.; Tunca, B.; Zarıfoglu, M.; Elibol, B.; Tokcaer, A.B.; Saka, E.; Demirkiran, M.; et al. Epigenetic approach to early-onset Parkinson’s disease: Low methylation status of SNCA and PARK2 promoter regions. Neuro. Res. 2017, 39, 965–972. [CrossRef]
44. Taskesen, E.; Mishra, A.; van der Sluis, S.; Ferrari, R.; International FTD-Genomics Consortium; Veldink, J.H.; van Es, M.A.; Smit, A.B.; Posthuma, D.; Pijnenburg, Y. Susceptible genes and disease mechanisms identified in frontotemporal dementia and frontotemporal dementia with Amyotrophic Lateral Sclerosis by DNA-methylation and GWAS. Sci. Rep. 2017, 7, 8899. [CrossRef] [PubMed]
45. Ebbert, M.; Ross, C.A.; Pregent, L.J.; Lank, R.J.; Zhang, C.; Katzman, R.B.; Jansen-West, K.; Song, Y.; da Rocha, E.L.; Palmucci, C.; et al. Conserved DNA methylation combined with differential frontal cortex and cerebellar expression distinguishes C9orf72-associated and sporadic ALS, and implicates SERPINA1 in disease. Acta Neuropathol. 2017, 134, 715–728. [CrossRef]
46. Kim, B.W.; Jeong, Y.E.; Wong, M.; Martin, L.J. DNA damage accumulates and responses are engaged in human ALS brain and spinal motor neurons and DNA repair is activatable in iPSC-derived motor neurons with SOD1 mutations. Acta Neuropathol. Commun. 2020, 8, 7. [CrossRef]
47. Bai, G.; Cheung, I.; Shulha, H.P.; Coelho, J.E.; Li, P.; Dong, X.; Jakovcevski, M.; Wang, Y.; Grigorenko, A.; Jiang, Y.; et al. Epigenetic dysregulation of hairy and enhancer of split 4 (HES4) is associated with striatal degeneration in postmortem Huntington brains. Hum. Mol. Genet. 2014, 23, 1441–1456. [CrossRef]
48. Gutierrez, A.; Corey-Bloom, J.; Thomas, E.A.; Desplats, P. Evaluation of Biochemical and Epigenetic Measures of Peripheral Brain-Derived Neurotrophic Factor (BDNF) as a Biomarker in Huntington’s Disease Patients. Front. Mol. Neurosci. 2020, 12, 335. [CrossRef]
49. Bachman, M.; Uribe-Lewis, S.; Yang, X.; Williams, M.; Murrell, A.; Balasubramanian, S. 5-Hydroxymethylcytosine is a predominantly stable DNA modification. Nat. Chem. 2014, 6, 1049–1055. [CrossRef]
50. Ellison, E.M.; Abner, E.L.; Lovell, M.A. Multiregional analysis of global 5-methylcytosine and 5-hydroxymethylcytosine through-out the progression of Alzheimer’s disease. J. Neurochem. 2016, 140, 383–394. [CrossRef]
51. Kaut, O.; Kuchelmeister, K.; Moehl, C.; Wüllner, U. 5-methylcytosine and 5-hydroxymethylcytosine in brains of patients with multiple system atrophy and patients with Parkinson’s disease. J. Chem. Neuroanat. 2019, 96, 41–48. [CrossRef] [PubMed]
52. Laszlo, A.H.; Derrington, I.M.; Brinkerhoff, H.; Langford, K.W.; Nova, I.C.; Samson, J.M.; Bartlett, J.J.; Pavlenok, M.; Gundlach, J.H. Detection and mapping of 5-methylcytosine and 5-hydroxymethylcytosine with nanopore MspA. Proc. Natl. Acad. Sci. USA 2013, 110, 18904–18909. [CrossRef] [PubMed]
53. Hamzeyi, H.; Savaş, D.; Tunca, C.; Şen, N.E.; Gündoğdu Eken, A.; Şahbaz, I.; Calini, D.; Tiloca, I.; Ticozzi, N.; Ratti, A.; et al. Elevated Global DNA Methylation Is Not Exclusive to Amyotrophic Lateral Sclerosis and Is Also Ob-served in Spinocerebellar Ataxia Types 1 and 2. Neurodegener. Dis. 2018, 18, 38–48. [CrossRef] [PubMed]
54. Jackson, J.L.; Finch, N.A.; Baker, M.C.; Kachererus, J.M.; DeJesus-Hernandez, M.; Pereira, K.; Christopher, E.; Prudencio, M.; Heckman, M.G.; Thompson, S.E.; et al. Elevated methylation levels, reduced expression levels, and frequent contractions in a clinical cohort of C9orf72 expansion carriers. Mol. Neurodegener. 2020, 15, 7. [CrossRef] [PubMed]
55. Zhang, M.; Tartaglia, M.C.; Moreno, D.; Sato, C.; McKeever, P.; Weichert, A.; Keith, J.; Robertson, J.; Zimmel, L.; Rogaeva, E. DNA methylation age-acceleration is associated with disease duration and age at onset in C9orf72 patients. Acta. Neuropathol. 2017, 134, 271–279. [CrossRef]
56. Coppede, F.; Stocco, A.; Mosca, L.; Gallo, R.; Tarlalini, C.; Lunetta, C.; Marocchi, A.; Migliore, L.; Penco, S. Increase in DNA methylation in patients with amyotrophic lateral sclerosis carriers of not fully penetrant SOD1 mutations. Amyotroph. Lateral Scler. Front. Degener. 2018, 19, 93–101. [CrossRef]
57. Madrid, A.; Hogan, K.J.; Papale, L.A.; Clark, L.R.; Asthana, S.; Johnson, S.C.; Alisch, R.S. DNA Hypomethylation in Blood Links B3GALT4 and ZADH2 to Alzheimer’s Disease. J. Alzheimer’s Dis. 2018, 66, 927–934. [CrossRef]
58. Salcedo-Tacuma, D.; Melgarejo, J.D.; Ortega-Rojas, J.; Arboleda-Bustos, C.E.; Pardo-Turriago, R.; Arboleda, H. Differential Methylation Levels in CpGs of the BIN1 Gene in Individuals with Alzheimer Disease. Alzheimer Dis. Assoc. Disord. 2019, 33, 321–326. [CrossRef]
59. Li, K.-X.; Sun, Q.; Wei, L.-L.; Du, G.-H.; Huang, X.; Wang, J.-K. ERα Gene Promoter Methylation in Cognitive Function and Quality of Life of Patients with Alzheimer’s Disease. J. Geriatr. Psychiatry Neurol. 2019, 32, 221–228. [CrossRef]
61. Shao, Y.; Shaw, M.; Todd, K.; Khrestian, M.; D’Aleo, G.; Barnard, P.J.; Zahratka, J.; Pillai, J.; Yu, C.-E.; Keene, C.D.; et al. DNA methylation of TOMM40-APOE-APOC2 in Alzheimer’s disease. *J. Hum. Genet.* 2018, 63, 459–471. [CrossRef] [PubMed]

62. Kobayashi, N.; Shinagawa, S.; Nagata, T.; Shimada, K.; Shibata, N.; Ohnuma, T.; Kasanuki, K.; Araí, H.; Yamada, H.; Nakayama, K.; et al. Usefulness of DNA Methylation Levels in COASY and SPINT1 Gene Promoter Regions as Biomarkers in Diagnosis of Alzheimer’s Disease and Amnestic Mild Cognitive Impairment. *PLoS ONE* 2016, 11, e0168816. [CrossRef] [PubMed]

63. Ozaki, Y.; Yoshino, Y.; Yamazaki, K.; Ochi, S.; Iga, J.; Nagai, M.; Nomoto, M.; Ueno, S. DRD2 methylation to differentiate dementia with Lewy bodies from Parkinson’s disease. *Acta Neurol. Scand.* 2019, 141, 177–182. [CrossRef] [PubMed]

64. Cohen-Hadad, Y.; Altarescu, G.; Eldar-Geva, T.; Levi-Lahad, E.; Zhang, M.; Rogaeva, E.; Gotkine, M.; Bartok, O.; Ashwal-Fluss, R.; Kadner, S.; et al. Marked Differences in C9orf72 Methylation Status and Isoform Expression between C9/ALS Human Embryonic and Induced Pluripotent Stem Cells. *Stem Cell Rep.* 2016, 7, 927–940. [CrossRef]

65. Kantor, B.; Tagliaferro, L.; Gu, J.; Zamora, M.E.; Illich, E.; Grenier, C.; Huang, Z.Y.; Murphy, S.; Chiba-Falek, O. Downregulation of SNCA Expression by Targeted Editing of DNA Methylation: A Potential Strategy for Precision Therapy in PD. *Mol. Ther.* 2018, 26, 2638–2649. [CrossRef]

66. Park, H.; Shin, J.; Kim, Y.; Saito, T.; Saito, T.C.; Kim, J. CRISPR/dCas9-Dnmt3a-mediated targeted DNA methylation of APP rescues brain pathology in a mouse model of Alzheimer’s disease. *Trans. Neurodegener.* 2022, 11, 41. [CrossRef]

67. Stoccoro, A.; Mosca, L.; Carnicelli, V.; Cavalli, U.; Lunetta, C.; Marocchi, A.; Migliore, L.; Coppè, F. Mitochondrial DNA copy number and D-loop region methylation in carriers of amyotrophic lateral sclerosis gene mutations. *Epigenomics* 2018, 10, 1431–1443. [CrossRef]

68. Xu, Y.; Xu, L.; Han, M.; Liu, X.; Li, F.; Zhou, X.; Wang, Y.; Bi, J. Altered mitochondrial DNA methylation and mitochondrial DNA copy number in an APP/PS1 transgenic mouse model of Alzheimer disease. *Biochem. Biophys. Res. Commun.* 2019, 520, 41–46. [CrossRef]

69. Marzi, S.; Leung, S.K.; Ribarska, T.; Hannon, E.; Smith, A.R.; Pishva, E.; Poschmann, J.; Moore, K.; Troakes, C.; Al-Sarraj, S.; et al. A histone acetylome-wide association study of Alzheimer’s disease identifies disease-associated H3K27ac differences in the entorhinal cortex. *Nat. Neurosci.* 2020, 23, 1618–1627. [CrossRef]

70. Klein, H.-U.; McCabe, C.; Gjoneska, E.; Sullivan, S.E.; Kaskow, B.J.; Tang, A.; Smith, R.V.; Xu, J.; Pfenning, A.R.; Bernstein, B.E.; et al. Epigenome-wide study uncovers large-scale changes in histone acetylation driven by tau pathology in aging and Alzheimer’s human brains. *Nat. Neurosci.* 2018, 22, 37–46. [CrossRef]

71. Park, G.; Tan, J.; Garcia, G.; Kang, Y.; Salvesen, G.; Zhang, Z. Regulation of Histone Acetylation by Autophagy in Parkinson Disease. *J. Biol. Chem.* 2016, 291, 3531–3540. [CrossRef] [PubMed]

72. Yakhine-Diop, S.M.S.; Niso-Santano, M.; Rodriguez-Arribas, M.; Gómez-Sánchez, R.; Martinez-Chacón, G.; Uribe-Carretero, E.; Navarro-García, J.A.; Ruiz-Hurtado, G.; Aiastui, A.; Cooper, J.M.; et al. Impaired Mitophagy and Protein Acetylation Levels in Fibroblasts from Parkinson’s Disease Patients. *Mol. Neurobiol.* 2019, 56, 2466–2481. [CrossRef] [PubMed]

73. Schueller, E.; Paiva, I.; Blanc, F.; Wang, X.L.; Cassel, J.C.; Boutillier, A.L.; Bousiges, O. Dysregulation of histone acetylation pathways in hippocampus and frontal cortex of Alzheimer’s disease patients. *Eur. Neuropsychopharmacol.* 2020, 33, 101–116. [CrossRef] [PubMed]

74. Mahady, L.; Nadeem, M.; Malek-Ahmadi, M.; Chen, K.; Perez, S.E.; Mufson, E.J. HDAC 2 dysregulation in the nucleus basalis of Meynert during the progression of Alzheimer’s disease. *Neuropathol. Appl. Neurobiol.* 2019, 45, 380–397. [CrossRef] [PubMed]

75. Tan, Y.; Delvaux, E.; Nolz, J.; Coleman, P.D.; Chen, S.; Mastroeni, D. Upregulation of histone deacetylase 2 in laser capture nigral microglia in Parkinson’s Disease. *Neuropathol. Aging*. 2018, 68, 134–141. [CrossRef]

76. Wu, Q.; Yang, X.; Zhang, L.; Zhang, Y.; Feng, L. Nuclear Accumulation of Histone Deacetylase 4 (HDAC4) Exerts Neurotoxicity in Models of Parkinson’s Disease. *Mol. Neurobiol.* 2017, 54, 6970–6983. [CrossRef] [PubMed]

77. Buovinicino, D.; Felici, R.; Ranieri, G.; Caramelli, R.; Lapucci, A.; Cavone, L.; Muzzi, M.; Di Pietro, L.; Bernardini, C.; Zwergel, R.; et al. Effects of Class II Selective Histone Deacetylase Inhibitor on Neuromuscular Function and Disease Progression in SOD1-ALS Mice. *Neuroscience* 2018, 379, 228–238. [CrossRef]

78. Lapucci, A.; Cavone, L.; Buovinicino, D.; Felici, R.; Gerace, E.; Zwergel, C.; Valente, S.; Mai, A.; Chiarami, A. Effect of Class II HDAC inhibition on glutamate transporter expression and survival in SOD1-ALS mice. *Neurosci. Lett.* 2017, 656, 120–125. [CrossRef]

79. Pegoraro, V.; Marozzo, R.; Angelini, C. MicroRNAs and HDAC4 protein expression in the skeletal muscle of ALS patients. *Clin. Neuropathol.* 2020, 39, 105–114. [CrossRef]

80. Pigna, E.; Simonazzi, E.; Sanna, K.; Bernadzki, K.M.; Proszynski, T.; Heil, C.; Palacios, D.; Adamo, S.; Moresi, V. Histone deacetylation 4 protects from degeneration and skeletal muscle atrophy in a murine model of amyotrophic lateral sclerosis. *eBioMedicine* 2019, 40, 717–732. [CrossRef]

81. Dios, A.M.; Babu, S.; Granucci, E.J.; Mueller, K.; Mills, A.; Alshikho, M.J.; Zürcher, N.R.; Cernasov, P.; Gilbert, T.; Glass, J.D.; et al. Class I and II histone deacetylation expression is not altered in human amyotrophic lateral sclerosis: Neuropathological and positron emission tomography molecular neuroimaging evidence. *Muscle Nerve* 2019, 60, 443–452. [CrossRef] [PubMed]

82. Boutillier, A.-L.; Tzeplaeff, L.; Dupuis, L. The dark side of HDAC inhibition in ALS. *eBioMedicine* 2019, 41, 38–39. [CrossRef]

83. Janczura, K.J.; Olmar, C.H.; Sartor, G.C.; Rao, S.J.; Ricciardi, N.R.; Lambert, G.; Brothers, S.P.; Wahlestedt, C. Inhibition of HDAC3 reverses Alzheimer’s disease-related pathologies in vitro and in the 3xTg-AD mouse model. *Proc. Natl. Acad. Sci. USA* 2018, 115, E11148–E11157. [CrossRef] [PubMed]
84. Esteves, A.; Palma, A.; Gomes, R.; Santos, D.; Silva, D.; Cardoso, S. Acetylation as a major determinant to microtubule-dependent autophagy: Relevance to Alzheimer’s and Parkinson disease pathology. *Biochim. Biophys. Acta (BBA) Mol. Basis Dis.* 2018, 1865, 2008–2023. [CrossRef] [PubMed]

85. Choi, H.; Kim, H.J.; Yang, J.; Chae, S.; Lee, W.; Chung, S.; Kim, J.; Choi, H.; Song, H.; Lee, C.K.; et al. Acetylation changes tau interactome to degrade tau in Alzheimer’s disease animal and organoid models. *Ageing Cell.* 2020, 19, e13081. [CrossRef]

86. Jian, W.; Wei, X.; Chen, L.; Wang, Z.; Sun, Y.; Zhu, S.; Lou, H.; Yan, S.; Li, X.; Zhou, J.; et al. Inhibition of HDAC6 increases acetylation of peroxiredoxin 1/2 and ameliorates 6-OHDA induced dopaminergic injury. *Neurosci. Lett.* 2017, 658, 114–120. [CrossRef]

87. Kim, T.; Song, S.; Park, S.; Seo, H. HDAC inhibition by valproic acid induces neuroprotection and improvement of PD-like behaviors in LRRK2 R1441G transgenic mice. *Exp. Neurol.* 2019, 28, 504–515. [CrossRef]

88. Harrison, I.F.; Smith, A.D.; Dexter, D.T. Pathological histone acetylation in Parkinson’s disease: Neuroprotection and inhibition of microglial activation through SIRT 2 inhibition. *Neurosci. Lett.* 2017, 666, 48–57. [CrossRef]

89. Esteves, A.R.; Arduini, D.M.; Silva, D.F.; Viana, S.D.; Pereira, F.C.; Cardoso, S.M. Mitochondrial Metabolism Regulates Microtubule Acetylation and Autophagy Through Sirtuin-2: Impact for Parkinson’s Disease. *Mol. Neurobiol.* 2018, 55, 1440–1462. [CrossRef]

90. Kuta, R.; Larchelle, N.; Fernandez, M.; Pal, A.; Minotti, S.; Tibshirani, M.; St.Louis, K.; Gentil, B.J.; Nalbantoglu, J.N.; Hermann, A.; et al. Depending on the stress, histone deacetylase inhibitors act as heat shock protein co-inducers in motor neurons and potentiate arimoclomol, exerting neuroprotection through multiple mechanisms in ALS models. *Cell Stress Chaperones* 2020, 25, 173–191. [CrossRef]

91. Rossaert, E.; Pollari, E.; Jaspers, T.; van Helleputte, L.; Jarpe, M.; van Damme, P.; de Bock, K.; Moisse, M.; van den Bosch, L. Restoration of histone acetylation ameliorates disease and metabolic abnormalities in a FUS mouse model. *Acta Neuropathol. Commun.* 2019, 7, 107. [CrossRef] [PubMed]

92. Guo, W.; Naujock, M.; Fumagalli, L.; Vandoorne, T.; Baatsen, P.; Boon, R.; Or dováš, L.; Patel, A.; Welters, M.; Vanwelden, T.; et al. HDAC6 inhibition reverses axonal transport defects in motor neurons derived from FUS-ALS patients. *Nat. Commun.* 2017, 8, 861. [CrossRef] [PubMed]

93. Guo, W.; Bosch, L.V.D. Therapeutic potential of HDAC6 in amyotrophic lateral sclerosis. *Cell Stress* 2018, 2, 14–16. [CrossRef] [PubMed]

94. Siebzehnrübl, F.A.; Raber, K.A.; Urbach, Y.K.; Schulze-Krebs, A.; Canneva, F.; Moceri, S.; Habermeyer, J.; Achoui, D.; Gupta, B.; Steinler, A.I.; Hayden, M.R.; et al. Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition. *Proc. Natl. Acad. Sci. USA* 2018, 115, E8765–E8774. [CrossRef] [PubMed]

95. Chopra, V.; Quinti, L.; Khanna, P.; Paganetti, P.; Kuhn, R.; Kazantsev, A.G.; Hersch, S. LBH589, A Hydroxamic Acid-Derived HDAC Inhibitor, is Neuroprotective in Mouse Models of Huntington’s Disease. *J. Huntington’s Dis.* 2016, 5, 347–355. [CrossRef]

96. Jia, H.; Morris, C.D.; Williams, R.M.; Loring, J.F.; Thomas, E.A. HDAC inhibition imparts beneficial transgenerational effects in Huntington’s disease mice via altered DNA and histone methylation. *Proc. Natl. Acad. Sci. USA* 2014, 112, E56–E64. [CrossRef]

97. Naia, L.; Cunha-Oliveira, T.; Rodrigues, J.; Rosenstock, T.R.; Oliveira, A.; Ribeiro, M.; Carmo, C.; Oliveira-Sousa, S.I.; Duarte, A.I.; Hayden, M.R.; et al. Histone Deacetylase Inhibitors Protect Against Pyruvate Dehydrogenase Dysfunction in Huntington’s Disease. *J. Neurosci.* 2017, 37, 2776–2794. [CrossRef]

98. Federspiel, J.D.; Greco, T.M.; Lum, K.K.; Cristea, I.M. Hdac4 Interactions in Huntington’s Disease Viewed Through the Prism of Multimomics. *Mult. Cell. Prot. Compon.* 2019, 18, S92–S113. [CrossRef]

99. Moreno, C.L.; Ehrlich, M.E.; Mobbs, C.V. Protection by dietary restriction in the YAC128 mouse model of Huntington’s disease: Relation to genes regulating histone acetylation and HTT. *Neurobiol. Dis.* 2016, 85, 25–34. [CrossRef]

100. Jia, H.; Wang, Y.; Morris, C.D.; Jacques, V.; Gottesfeld, J.; Rusche, J.R.; Thomas, E.A. The Effects of Pharmacological Inhibition of Histone Deacetylase 3 (HDAC3) in Huntington’s Disease Mice. *PLoS ONE* 2016, 11, e0152498. [CrossRef]

101. Suelves, N.; Kirkham-McCarthy, L.; Lahue, R.S.; Ginés, S. A selective inhibitor of histone deacetylase 3 prevents cognitive deficits and suppresses striatal CAG repeat expansions in Huntington’s disease mice. *Sci. Rep.* 2017, 7, 6082. [CrossRef]

102. Ragot, A.; Pietropaolo, S.; Vincent, J.; Delage, P.; Zhang, H.; Allinquant, B.; Leinekugel, X.; Fischer, A.; Cho, Y.H. Genetic deletion of the Histone Deacetylase 6 exacerbates selected behavioral deficits in the R6/1 mouse model for Huntington’s disease. *Brain Behav.* 2015, 5, e00361. [CrossRef] [PubMed]

103. Dong, X.; Tsuiji, J.; Labadorf, A.; Roussos, P.; Chen, J.-F.; Myers, R.H.; Akbarian, S.; Weng, Z. The Role of H3K4me3 in Transcriptional Regulation Is Altered in Huntington’s Disease. *PLoS ONE* 2015, 10, e0144398. [CrossRef]

104. Song, W.; Zsindely, N.; Faragó, A.; Marsh, J.L.; Bodai, L. Systematic genetic interaction studies identify histone demethylase Utx as potential target for ameliorating Huntington’s disease. *Hum. Mol. Genet.* 2017, 27, 649–666. [CrossRef] [PubMed]

105. Lee, J.; Hwang, Y.J.; Kim, Y.; Lee, M.; Hyeon, S.J.; Lee, S.; Kim, D.H.; Jang, S.; Im, H.; Min, S.-J.; et al. Remodeling of heterochromatin structure slows neuropathological progression and prolongs survival in an animal model of Huntington’s disease. *Acta Neuropathol.* 2017, 134, 729–748. [CrossRef] [PubMed]

106. March, Z.M.; King, O.D.; Shorter, J. Prion-like domains as epigenetic regulators, scaffolds for subcellular organization, and drivers of neurodegenerative disease. *Brain Res.* 2016, 1647, 9–18. [CrossRef] [PubMed]

107. Chen-Plotkin, A.S.; Lee, V.M.-Y.; Trojanowski, J.Q. TAR DNA-binding protein 43 in neurodegenerative disease. *Nat. Rev. Neuro.* 2010, 6, 211–220. [CrossRef] [PubMed]

108. Guo, W.; Shorter, J. Biology and Pathobiology of TDP-43 and Emergent Therapeutic Strategies. *Cold Spring Harb. Perspect. Med.* 2016, 7, a024554. [CrossRef]
109. Harrison, A.F.; Shorter, J. RNA-binding proteins with prion-like domains in health and disease. *Biochem. J.* 2017, 474, 1417–1438. [CrossRef]

110. Murakami, K.; Ono, K. Interactions of amyloid coaggregates with biomolecules and its relevance to neurodegeneration. *FASEB J.* 2022, 36, e22493. [CrossRef]

111. Henriques, A.D.; Machado-Silva, W.; Leite, R.E.P.; Suemoto, C.K.; Leite, K.R.M.; Srougi, M.; Pereira, A.C.; Jacob-Filho, W.; Nóbrega, O.T. Genome-wide profiling and predicted significance of post-mortem brain microRNA in Alzheimer’s disease. *Mech. Aging Dev.* 2020, 191, 11352. [CrossRef] [PubMed]

112. Moradifard, S.; Hoseinbeiki, M.; Ganji, S.M.; Minuchehr, Z. Analysis of microRNA and Gene Expression Profiles in Alzheimer’s Disease: A Meta-Analysis Approach. *Sci. Rep.* 2018, 8, 4767. [CrossRef] [PubMed]

113. Núñez-Iglesias, J.; Liu, C.-C.; Morgan, T.E.; Finch, C.E.; Zhou, X.J. Joint Genome-Wide Profiling of miRNA and mRNA Expression in Alzheimer’s Disease Cortex Reveals Altered miRNA Regulation. *PLoS ONE* 2010, 5, e8898. [CrossRef] [PubMed]

114. Watson, C.N.; Begum, G.; Ashman, E.; Thorn, D.; Yakoub, K.M.; Al Hariri, M.; Nehme, A.; Mondello, S.; Kobeissy, F.; Belli, A.; et al. Co-Expression Analysis of microRNome and Proteins in Brain of Alzheimer’s Disease Patients. *Cells* 2021, 11, 163. [CrossRef] [PubMed]

115. Ren, R.J.; Zhang, Y.F.; Dammer, E.B.; Zhou, Y.; Wang, L.L.; Liu, X.H.; Feng, B.L.; Jiang, G.X.; Chen, S.D.; Wang, G.; et al. Peripheral Blood MicroRNA Expression Profiles in Alzheimer’s Disease: Screening, Validation, Association with Clinical Phenotype and Implications for Molecular Mechanism. *Mol. Neurobiol.* 2016, 53, 5772–5781. [CrossRef]

116. Wang, Z.; Shen, L.; Wang, Y.; Huang, S. Integrated analysis of miRNA and mRNA expression in the blood of patients with Alzheimer’s disease. *Mol. Med. Rep.* 2020, 22, 1053–1062. [CrossRef]

117. Dong, H.; Li, J.; Huang, L.; Chen, X.; Li, D.; Wang, T.; Hu, C.; Xu, J.; Zhang, C.; Zen, K.; et al. Serum MicroRNA Profiles Serve as Novel Biomarkers for the Diagnosis of Alzheimer’s Disease. *Dis. Markers* 2015, 2015, 625659. [CrossRef]

118. Li, Z.-R.; Liu, R.; Zeng, L.; Jiang, H.-L.; Ashraf, G.M. MicroRNA and mRNA profiling of cerebral cortex in a transgenic mouse model of Alzheimer’s disease. *Sci. Rep.* 2018, 8, 3084–3094. [CrossRef]

119. McKeever, P.M.; Schneider, R.; Taghdirti, F.; Weichert, A.; Multani, N.; Brown, A.L.; Boxer, A.L.; Karydas, A.; Miller, B.; Robertson, J.; et al. MicroRNA Expression Levels Are Elevated in the Cerebrospinal Fluid of Patients with Young-Onset Alzheimer’s Disease. *Mol. Neurobiol.* 2018, 55, 8826–8841. [CrossRef] [PubMed]

120. Dong, Z.; Gu, H.; Guo, Q.; Liang, S.; Xue, J.; Yao, F.; Liu, X.; Li, F.; Liu, H.; Sun, L.; et al. Profiling of Serum Exosome MiRNA Reveals the Potential of a MiRNA Panel as Diagnostic Biomarker for Alzheimer’s Disease. *Mol. Neurobiol.* 2021, 58, 3004–3013. [CrossRef] [PubMed]

121. Serpente, M.; Fenoglio, C.; D’Anca, M.; Arcaro, M.; Sorrentino, F.; Visconte, C.; Arighi, A.; Fumagalli, G.G.; Porretti, L.; Cattaneo, A.; et al. MiRNA Profiling in Plasma Neural-Derived Small Extracellular Vesicles from Patients with Alzheimer’s Disease. *Ageing Dev.* 2020, 2, 2897–2920. [CrossRef] [PubMed]

122. Kurz, A.; Kumar, R.; Northoff, B.; Schirra, J.; Donakonda, S.; Hübner, R.; et al. Differential expression of gut miRNAs are altered in idiopathic Parkinson’s Disease. *Park. Relat. Disord.* 2021, 8, 46–50. [CrossRef]

123. Cardo, L.F.; Coto, E.; Ribacoba, R.; Moris, G.; Menéndez, M.; Álvarez, L.M. Profile of microRNAs in the plasma of Parkinson’s disease patients and healthy controls. *J. Neurol.* 2013, 260, 1420–1422. [CrossRef] [PubMed]

124. Raf, W.; Freischmidt, A.; Grotzhanov, V.; Roth, V.; Brockmann, S.; Mollenhauer, B.; Martin, D.; Haslinger, B.; Fundel-Clemens, K.; Otto, M.; et al. Protein Binding Partners of Dysregulated miRNAs in Parkinson’s Disease Serum. *Cells* 2021, 10, 791. [CrossRef] [PubMed]
134. dos Santos, M.C.T.; Barreto-Sanz, M.A.; Correia, B.R.S.; Bell, R.; Widnell, C.; Perez, L.T.; Berteau, C.; Schulte, C.; Scheller, D.; Berg, D.; et al. miRNA-based signatures in cerebrospinal fluid as potential diagnostic tools for early stage Parkinson’s disease. *Oncotarget* 2018, 9, 17455–17465. [CrossRef] [PubMed]

135. Mo, M.; Xiao, Y.; Huang, S.; Cen, L.; Chen, X.; Zhang, L.; Luo, Q.; Li, S.; Yang, X.; Lin, X.; et al. MicroRNA expression profiles in A53T mutant alpha-synuclein transgenic mice and Parkinsonian. *Oncotarget* 2016, 8, 15–28. [CrossRef]

136. Jiang, Y.; Chen, J.; Sun, Y.; Li, F.; Wei, L.; Sun, W.; Deng, J.; Yuan, Y.; Wang, Z. Profiling of Differentially Expressed MicroRNAs in Saliva of Parkinson’s Disease Patients. *Front. Neurol.* 2021, 12, 738530. [CrossRef]

137. He, S.; Huang, L.; Shao, C.; Nie, T.; Xia, L.; Cui, B.; Lu, F.; Zhu, L.; Chen, B.; Yang, Q. Several miRNAs derived from serum extracellular vesicles are potential biomarkers for early diagnosis and progression of Parkinson’s disease. *Transl. Neurodegener.* 2021, 10, 25. [CrossRef]

138. Yadav, S.K.; Pandey, A.; Sarkar, S.; Yadav, S.S.; Parmar, D.; Yadav, S. Identification of Altered Blood MicroRNAs and Plasma Proteins in a Rat Model of Parkinson’s Disease. *Mol. Neurobiol.* 2022, 59, 1781–1798. [CrossRef]

139. Tolosa, E.; Botta-Orfila, T.; Morató, X.; Calatauyud, C.; Ferrer-Lorente, R.; Marti, M.J.; Fernández, M.; Gaig, C.; Raya, A.; Consiglio, A.; et al. MicroRNA alterations in iPSC-derived dopaminergic neurons from Parkinson disease patients. *Neurobiol. Aging* 2018, 69, 283–291. [CrossRef]

140. Campos-Melo, D.; Droppelmann, C.A.; He, Z.; Volk, K.; Strong, M.J. Altered microRNA expression profile in amyotrophic lateral sclerosis: A role in the regulation of NFL mRNA levels. *Mol. Brain* 2013, 6, 26. [CrossRef]

141. Wakabayashi, K.; Mori, F.; Kakita, A.; Takahashi, H.; Utsumi, J.; Sasaki, H. Analysis of microRNA from archived formalin-fixed paraffin-embedded specimens of amyotrophic lateral sclerosis. *Acta Neuropathol. Commun.* 2014, 2, 173. [CrossRef] [PubMed]

142. Aksu-Menges, E.; Balci-Hayta, B.; Bekircan-Kurt, C.E.; Aydinoglu, A.T.; Erdem-Ozdamar, S.; Tan, E. Two distinct skeletal muscle microRNA signatures revealing the complex mechanism of sporadic ALS. *Acta Neurol. Belg.* 2021, 1–11. [CrossRef] [PubMed]

143. De Felice, B.; Manfelliott, F.; Fiorentino, G.; Annunziata, A.; Biffali, E.; Pannone, R.; Federico, A. Wide-Ranging Analysis of MicroRNA Profiles in Sporadic Amyotrophic Lateral Sclerosis Using Next-Generation Sequencing. *Front. Genet.* 2018, 9, 310. [CrossRef] [PubMed]

144. Chen, Y.; Wei, Q.; Chen, X.; Li, C.; Cao, B.; Ou, R.; Hadano, S.; Shang, H.-F. Aberration of miRNAs Expression in Leukocytes from Sporadic Amyotrophic Lateral Sclerosis. *Front. Mol. Neurosci.* 2018, 69, 69. [CrossRef] [PubMed]

145. De Felice, B.; Guida, M.; Guida, M.; Coppola, C.; de Mieri, G.; Cotrufo, R. A miRNA signature in leukocytes from sporadic amyotrophic lateral sclerosis. *Gene* 2018, 508, 35–40. [CrossRef]

146. Liguori, M.; Nuzziello, N.; Introna, A.; Consiglio, A.; Licciulli, F.; D’Errico, E.; Scarafino, A.; Distaso, E.; Simone, I.L. Dysregulation of MicroRNAs and Target Genes Networks in Peripheral Blood of Patients With Sporadic Amyotrophic Lateral Sclerosis. *Front. Mol. Neurosci.* 2018, 11, 288. [CrossRef]

147. Takahashi, I.; Hama, Y.; Matsushima, M.; Hirotani, M.; Kano, T.; Hohzen, H.; Yabe, I.; Utsumi, J.; Sasaki, H. Identification of plasma microRNAs as a biomarker of sporadic Amyotrophic Lateral Sclerosis. *Mol. Brain* 2015, 8, 67. [CrossRef]

148. Freischmidt, A.; Müller, K.; Zondler, L.; Weydt, P.; Volk, A.E.; Božić, A.L.; Walter, M.; Bonin, M.; Mayer, B.; von Arnim, C.A.F.; et al. Serum microRNAs in patients with genetic amyotrophic lateral sclerosis and pre-manifest mutation carriers. *Brain* 2014, 137, 2938–2950. [CrossRef] [PubMed]

149. Jollin, G.; Gray, E.; Thompson, A.G.; Bobeva, Y.; Talbot, K.; Weishaupt, J.; Ludolph, A.; Malaspina, A.; Leigh, P.N.; Newbury, S.F.; et al. Identification of a potential non-coding RNA biomarker signature for amyotrophic lateral sclerosis. *Brain Commun.* 2020, 2, fcaa053. [CrossRef]

150. Taguchi, Y.-H.; Wang, H. Exploring miRNA Biomarker for Amyotrophic Lateral Sclerosis. *Int. J. Mol. Sci.* 2018, 19, 1318. [CrossRef]

151. Benigni, M.; Ricci, C.; Jones, A.R.; Giannini, F.; Al-Chalabi, A.; Battistini, S. Identification of miRNAs as Potential Biomarkers in Cerebrospinal Fluid from Amyotrophic Lateral Sclerosis Patients. *NeuroMolecular Med.* 2016, 18, 551–560. [CrossRef] [PubMed]

152. Kats, M.; Hama, Y.; Utsumi, J.; Takashina, K.; Yasumatsu, H.; Mori, F.; Wakabayashi, K.; Shoji, M.; Sasaki, H. MicroRNA expression profiles of neuron-derived extracellular vesicles in plasma from patients with amyotrophic lateral sclerosis. *Neurosci. Lett.* 2019, 708, 134176. [CrossRef] [PubMed]

153. Lo, T.-W.; Figuerola-Romer, C.; Hur, J.; Pacut, C.; Stoll, E.; Spring, C.; Lewis, R.; Nair, A.; Goutman, S.A.; Sakowski, S.A.; et al. Extracellular Vesicles in Serum and Central Nervous System Tissues Contain microRNA Signatures in Sporadic Amyotrophic Lateral Sclerosis. *Front. Mol. Neurosci.* 2018, 14, 739016. [CrossRef] [PubMed]

154. Rizzuti, M.; Melzi, V.; Gagliardi, D.; Resnati, D.; Meneri, M.; Dionis, L.; Masrori, P.; Hersmus, N.; Poens, K.; Locatelli, M.; et al. Insights into the identification of a molecular signature for amyotrophic lateral sclerosis exploiting integrated microRNA profiling of iPSC-derived motor neurons and exosomes. *Cell. Mol. Life Sci.* 2022, 79, 189. [CrossRef]

155. Saucier, D.; Wajnberg, G.; Roy, J.; Beauregard, A.P.; Chacko, S.; Crapoulet, N.; Fourrier, S.; Ghosh, A.; Lewis, S.M.; Marrero, A.; et al. Identification of a circulating miRNA signature in extracellular vesicles collected from amyotrophic lateral sclerosis patients. *Brain Res.* 2019, 1708, 100–108. [CrossRef]

156. Toivonen, J.M.; Manzano, R.; Olíván, S.; Zaragoza, P.; García-Redondo, A.; Osta, R. MicroRNA-206: A Potential Circulating Biomarker Candidate for Amyotrophic Lateral Sclerosis. *PLoS ONE* 2014, 9, e89065. [CrossRef]

157. Matamala, J.M.; Arias-Carrasco, R.; Sanchez, C.; Uhrig, M.; Bargsted, L.; Matus, S.; Maracaja-Coutinho, V.; Abarzua, S.; van Zundert, B.; Verdugo, R.; et al. Genome-wide circulating microRNA expression profiling reveals potential biomarkers for amyotrophic lateral sclerosis. *Neurobiol. Aging* 2018, 64, 123–138. [CrossRef]
205. Tung, Y.-T.; Peng, K.-C.; Chen, Y.-C.; Yen, Y.-P.; Chang, M.; Thams, J.-A. Mir-17–92 Confers Motor Neuron Subtype Differential Resistance to ALS-Associated Degeneration. *Cell Stem Cell* 2019, 25, 193–209.e7. [CrossRef]

206. Segret, L.; Nair, S.S.; Dancourt, J.; Aaronson, J.; Rosinski, J.; Neri, C. Combining feature selection and shape analysis uncovers precise rules for miRNA regulation in Huntington’s disease mice. *BMC Bioinform.* 2020, 21, 75. [CrossRef]

207. Fukushima, M.; Takahashi, M.; Fujita, H.; Chiy, T.; Popiel, H.A.; Watanabe, S.; Furuya, H.; Murata, M.; Wada, K.; Okada, T.; et al. Supplemental Treatment for Huntington’s Disease with miR-132 that Is Deficient in Huntington’s Disease Brain. *Mol. Ther. Nucleic Acids* 2018, 11, 79–90. [CrossRef]

208. Kunkanjanawan, T.; Carter, R.L.; Prucha, M.S.; Yang, J.; Parnpai, R.; Chan, A.W.S. miR-196a Ameliorates Cytotoxicity and Cellular Phenotype in Transgenic Huntington’s Disease Motor Neuron Cells. *PLoS ONE* 2016, 11, e0162788. [CrossRef]

209. Her, L.-S.; Mao, S.-H.; Chang, C.-Y.; Cheng, P.-H.; Chang, Y.-F.; Yang, H.-J.; Chen, C.-M.; Yang, S.-H. miR-196a Enhances Neuronal Morphology through Suppressing RANBP10 to Provide Neuroprotection in Huntington’s Disease. *Theranostics* 2017, 7, 2452–2462. [CrossRef]

210. Ban, J.-J.; Chung, J.-Y.; Lee, M.; Im, W.; Kim, M. MicroRNA-27a reduces mutant huntingtin aggregation in an in vitro model of Huntington’s disease. *Biochem. Biophys. Res. Commun.* 2017, 488, 316–321. [CrossRef]

211. Pfister, E.L.; DiNardo, N.; Mondo, E.; Borel, F.; Conroy, F.; Fraser, C.; Gernoux, G.; Han, X.; Hu, D.; Johnson, E.; et al. Artificial miRNAs Reduce Human Mutant Huntingtin Throughout the Striatum in a Transgenic Sheep Model of Huntington’s Disease. *Hum. Gene Ther.* 2018, 29, 663–673. [CrossRef] [PubMed]

212. Caron, N.S.; Southwell, A.L.; Brouwers, C.C.; Cengio, L.D.; Black, H.F.; Anderson, L.M.; Ko, S.; Zhu, X.; van Deventer, S.J.; et al. Potent and sustained huntingtin lowering via AA5 encoding miRNA preserves striatal volume and cognitive function in a humanized mouse model of Huntington disease. *Nucleic Acids Res.* 2019, 48, 36–54. [CrossRef] [PubMed]

213. Cordeiro, Y.; Macedo, B.; Silva, J.L.; Gomes, M.P.B. Pathological implications of nucleic acid interactions with proteins associated with neurodegenerative diseases. *Biophys. Rev.* 2014, 6, 97–110. [CrossRef] [PubMed]

214. Cordeiro, Y.; Silva, J.L. The Hypothesis of the Catalytic Action of Nucleic Acid on the Conversion of Prion Protein. *Protein Pept. Lett.* 2005, 12, 251–255. [CrossRef]

215. Macedo, B.; Millen, T.A.; Braga, C.A.C.A.; Gomes, M.P.B.; Ferreira, P.S.; Kraineva, J.; Winter, R.; Silva, J.; Cordeiro, Y. Nonspecific Prion Protein–Nucleic Acid Interactions Lead to Different Aggregates and Cytotoxic Species. *Biochemistry* 2012, 51, 5402–5413. [CrossRef]

216. Gomes, M.P.B.; Millen, T.A.; Ferreira, P.S.; e Silva, N.L.C.; Vieira, T.C.R.G.; Almeida, M.; Silva, J.L.; Cordeiro, Y. Prion Protein Complexed to N2a Cellular RNAs through Its N-terminal Domain Forms Aggregates and Is Toxic to Murine Neuroblastoma Cells. *J. Biol. Chem.* 2008, 283, 19616–19625. [CrossRef]

217. Tandon, A.; Subramani, V.K.; Kim, K.K.; Park, S.H. Interaction of Prion Peptides with DNA Structures. *Acta Neuropathol.* 2015, 129, 251–255. [CrossRef] [PubMed]

218. Adler, V.; Zeiler, B.; Kryukov, V.; Kascak, R.; Rubenstein, R.; Grossman, A. Small, highly structured RNAs participate in the conversion of human recombinant PrPSen to PrPRes in vitro. *J. Mol. Biol.* 2003, 332, 47–57. [CrossRef]

219. Deleault, N.R.; Lucassen, R.W.; Supattapone, S. RNA molecules stimulate prion protein conversion. *Nature* 2003, 425, 717–720. [CrossRef]

220. Mashima, T.; Nishikawa, F.; Kamatari, Y.O.; Fujitawa, H.; Saimura, M.; Nagata, T.; Kodaki, T.; Nishikawa, S.; Wu, K.; Katahira, M. Anti-prion activity of an RNA aptamer and its structural basis. *Nucleic Acids Res.* 2012, 41, 1355–1362. [CrossRef]

221. Dalai, W.; Matsuo, E.; Takeyama, N.; Kawano, J.; Saeki, K. CpG site DNA methylation patterns reveal a novel regulatory element in the mouse prion protein gene. *J. Vet. Med. Sci.* 2017, 79, 100–107. [CrossRef] [PubMed]

222. Dalai, W.; Matsuo, E.; Takeyama, N.; Kawano, J.; Saeki, K. Increased expression of prion protein gene is accompanied by demethylation of CpG sites in a mouse embryonal carcinoma cell line, P19C6. *J. Vet. Med. Sci.* 2017, 79, 644–648. [CrossRef] [PubMed]

223. Dabin, L.C.; Guntoro, F.; Campbell, T.; Belicard, T.; Smith, A.R.; Smith, R.G.; Raybould, R.; Schott, J.M.; Lunnon, K.; Sarkies, P.; et al. Altered DNA methylation profiles in blood from patients with sporadic Creutzfeldt–Jakob disease. *Acta Neuropathol.* 2020, 140, 863–879. [CrossRef] [PubMed]

224. Hernaiz, A.; Sanz, A.; Sentre, S.; Ranera, B.; Lopez-Perez, O.; Zaragoza, P.; Badiola, J.J.; Filali, H.; Boezaart, A.P.; et al. Genome-Wide Methylation Profiling in the Thalamus of Scapie Sheep. *Front. Vet. Sci.* 2020, 9, 824677. [CrossRef]

225. Gunter, F.; Viré, E.; Giordani, C.; Darwent, L.; Hummerich, H.; Linehan, J.; Sinka, K.; Jaunmuktane, Z.; Brandner, S.; Collinge, J.; et al. DNA methylation analysis of archival lymphoprepitate tissues in Creutzfeldt-Jakob disease. *Acta Neuropathol.* 2022, 144, 785–787. [CrossRef]

226. Harvey, Z.H.; Chakravarty, A.K.; Futia, R.A.; Jarosz, D.F. A Prion Epigenetic Switch Establishes an Active Chromatin State. *Cell 2020, 180, 928–940.e14. [CrossRef]

227. Zhu, T.; Zhao, S.; Liu, M.; Song, Z.; Yuan, Z.; Li, C.; Wang, Y.; Zhou, H.; Yin, X.; Hassan, M.F.; Yang, L. HDAC6 alleviates prion peptide-mediated neuronal death via modulating PI3K-Akt-mTOR pathway. *Neurobiol. Aging* 2016, 37, 91–102. [CrossRef]

228. Seo, J.-S.; Moon, M.-H.; Jeong, J.-K.; Seol, J.-W.; Lee, Y.-J.; Park, B.-H.; Park, S.-Y. SIRT1, a histone deacetylase, regulates prion protein-induced neuronal cell death. *Neurobiol. Aging* 2012, 33, 1110–1120. [CrossRef]

229. Jeong, J.-K.; Moon, M.-H.; Lee, Y.-J.; Seol, J.-W.; Park, S.-Y. Autophagy induced by the class III histone deacetylase Sirt1 prevents prion peptide neurotoxicity. *Neurobiol. Aging* 2012, 34, 146–156. [CrossRef]
230. Wang, J.; Zhang, J.; Shi, Q.; Zhang, B.-Y.; Chen, C.; Chen, L.-N.; Sun, J.; Wang, H.; Xiao, K.; Dong, X.-P. Scrapie Infection in Experimental Rodents and SMB-S15 Cells Decreased the Brain Endogenous Levels and Activities of Sirt1. J. Mol. Neurosci. 2014, 55, 1022–1030. [CrossRef]

231. Boese, A.S.; Saba, R.; Campbell, K.; Majer, A.; Medina, S.; Burton, L.; Booth, T.F.; Chong, P.; Westmacott, G.; Dutta, S.M.; et al. MicroRNA abundance is altered in synaptoneurosomes during prion disease. Mol. Cell. Neurosci. 2016, 71, 13–24. [CrossRef] [PubMed]

232. Gao, C.; Wei, J.; Zhang, B.-Y.; Shi, Q.; Chen, C.; Wang, J.; Shi, Q.; Dong, X.-P. miRNA expression profiles in the brains of mice infected with scrapie agents 139A, ME7 and S15. Emerg. Microbes Infect. 2016, 5, 1–10. [CrossRef] [PubMed]

233. Toivonen, J.M.; Sanz-Rubio, D.; López-Pérez, Ó.; Marín-Moreno, A.; Bolea, R.; Osta, R.; Badiola, J.J.; Zaragoza, P.; Espinosa, J.-C.; Torres, J.-M.; et al. MicroRNA Alterations in a Tg501 Mouse Model of Prion Disease. Biomolecules 2020, 10, 908. [CrossRef] [PubMed]

234. Slota, J.; Medina, S.J.; Klassen, M.; Gorski, D.; Mesa, C.M.; Robertson, C.; Mitchell, G.; Coulthart, M.B.; Pritzkow, S.; Soto, C.; et al. Identification of circulating microRNA signatures as potential biomarkers in the serum of elk infected with chronic wasting disease. Sci. Rep. 2019, 9, 19705. [CrossRef]

235. Rubio, D.S.; López-Pérez, Ó.; de Andrés Pablo, A.; Bolea, R.; Osta, R.; Badiola, J.J.; Zaragoza, P.; Martín-Burriel, I.; Toivonen, J.M. Increased circulating microRNAs miR-342-3p and miR-21-5p in natural sheep prion disease. J. Gen. Virol. 2017, 98, 305–310. [CrossRef]

236. Pease, D.; Scheckel, C.; Schaper, E.; Eckhardt, V.; Emmenegger, M.; Xenarios, I.; Aguzzi, A. Genome-wide identification of microRNAs regulating the human prion protein. Brain Pathol. 2018, 29, 232–244. [CrossRef]

237. Burak, K.; Lamoureux, L.; Boese, A.; Majer, A.; Saba, R.; Niu, Y.; Frost, K.; Booth, S.A. MicroRNA-16 targets mRNA involved in neurite extension and branching in hippocampal neurons during presymptomatic prion disease. Neurobiol. Dis. 2018, 112, 1–13. [CrossRef]

238. Gao, C.; Shi, Q.; Wei, J.; Zhou, W.; Xiao, K.; Wang, J.; Shi, Q.; Dong, X.-P. The associations of two SNPs in miRNA-146a and one SNP in ZBTB38-RASA2 with the disease susceptibility and the clinical features of the Chinese patients of sCJD and FFI. Prion 2018, 12, 34–41. [CrossRef]

239. Kang, S.-G.; Kim, C.; Aiken, J.; Yoo, H.S.; McKenzie, D. Dual MicroRNA to Cellular Prion Protein Inhibits Propagation of Pathogenic Prion Protein in Cultured Cells. Mol. Neurobiol. 2017, 55, 2384–2396. [CrossRef]