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Review

Transgenic Mouse Models for the Study of Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases (NDs) are some of the most important health challenges modern medicine and advanced societies face. Indeed, the number of patients affected by one of these illnesses will increase in the following years at the same rate that human life expectancy allows us to live longer. Despite many years of research, NDs remain invariably fatal. A complete understanding of the exact mechanisms leading to neuronal death, which will ideally allow preclinical detection and the development of effective treatments, has not yet been achieved. However, a great deal of information about ND pathology and the search for possible therapies has been acquired using animal models and more precisely transgenic mouse models. In this review, the main contributions of these powerful research tools in NDs as well as their advantages and caveats are discussed.

Keywords: neurodegenerative diseases; transgenic mice

1. Introduction

Human life has been extended in the last decades thanks to modern medicine and general improvement in human life quality. However, the increase in our life expectancy has resulted in a new major challenge for human health: neurodegenerative diseases (ND) in the elderly. Diseases involving the loss of nerve cells are currently a main problem in the aging population worldwide, which will go worse since a further rise in human longevity is expected, especially in developed countries. For instance, Alzheimer's disease (AD) is believed to affect around 40 million people worldwide and its prevalence is expected to reach 135 million people by 2050 [1]. In addition, NDs truly disable patients causing great suffering to them, their relatives, and their caretakers affecting seriously not only the physical but also the mental health of all people involved.

Despite the huge amounts of funds, human effort, and the years passed, NDs do not have an effective treatment. Few drugs for treating symptoms at the beginning of the disease course have been approved. For example, the L-DOPA-based treatment of Parkinson's disease (PD) therapies substitutes dopamine precursors due to the death of dopaminergic neurons, but its efficiency is temporal and limited [2]. The lack of success in the search for ND's treatment is partially influenced by the incubation time of NDs. The molecular events that trigger neuron death start years (even decades) before symptom appearance. Central nervous system (CNS) plasticity, which allows neuronal web reconnection and reconfiguration when cells die to maintain the system function, disguises the disease. Thus, NDs might be already irreversible at symptom onset. A possible option to improve the chances of successful therapies will be to direct them to the preclinical phase of these diseases, although treatment after the onset of clinical symptoms is the most common scenario in NDs. Such situations point out the need for models for NDs, both to understand the basis of the underlying pathology and to test potential drugs.

Most common NDs share in the center of their pathology the aggregation of a misfolded protein, as well as an unknown and complicated etiology in the majority of the patients. The first animal models for the study of NDs were knock-out (KO) mice, aimed to recapitulate the loss-of-function of the genes coding the proteins that get aggregated. Mice's advantages concerning other animals include their small size, short lifespan and generation time, easy manipulation, and availability of well-established molecular biology techniques that allow genetic manipulation. In addition, many tests aimed to check several aspects of human behavior have been established and normalized in rodents. Thus, transgenic mice have been implemented as the preferred animal model for the study of NDs. The later development of homologous recombination-mediated genetic engineering further facilitated transgenic mice creation [3] by targeting particular cell populations and allowing spatiotemporal expression of the transgenes. The existence of genetically inherited forms of certain NDs also facilitated the generation of transgenic mice models for disease study and therapy assessment. However, a general problem with transgenic mice models of NDs is that they often do not completely recapitulate the whole human phenotype, making the available models just partially useful. The very

recent development of the simple and powerful CRISPR-Cas9 for gene editing is called to revolutionize and improve transgenic animal creation [4]. New models for NDs are already being produced by this technique and their utility shall therefore be compared to that of the currently existing ones in the future.

This review aims to compile the most relevant transgenic mice models for several NDs, their success and pitfalls, and discuss the currently unsolved problems in NDs modeling.

2. Transgenic Mouse Models for the Study of Synucleinopathies

Synucleinopathies are a group of NDs which are molecularly characterized by the CNS accumulation of α-synuclein (α-syn) intracytoplasmic inclusions. Synucleinopathies include Parkinson's disease (PD), dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA). Although α-syn is involved in all cases, the most affected brain areas and specific cell types differ between diseases, influencing the clinical signs associated with each pathology.

2.1 Parkinson's Disease (PD)

PD is the most prevalent synucleinopathy [5] and the most common ND movement disorder, affecting around 1.2 million people in Europe [6]. It was predicted that around 9 million people worldwide will be affected by PD in 2030 [7]. PD is characterized by motor symptoms like rigidity, tremor, postural instability, and bradykinesia due to the loss of dopaminergic neurons in the substantia nigra pars compacta projecting to the CNS striatum [8]. Other non-motor symptoms include lack of motivation, depression, sleep disorders, cognitive impairment, loss of smell, and constipation [9–11]. α-syn inclusions detected in the cytoplasm of neurons, Lewy Bodies (LBs), are the major histopathological hallmark of PD [12–14]. In addition, α-syn inclusions can be found in so-called Lewy neurites (LNs) [14]. In healthy individuals, α-syn is located at great amounts in the presynaptic terminals in equilibrium between monomeric, oligomeric, and aggregated forms [15]. However, in PD patients, LBs and LNs form and spread through neurons [16–18]. Current evidence supports that LBs and LNs are not the toxic components responsible for neuron death, but may cause functional deficits [19,20].

Most PD cases are of unknown etiology, however, there are familial forms of PD that correlate with mutations in several genes such as *SNCA*, *PARK2*, *UCHL1*, *PINK1*, *DJ-1*, and *LRRK2* [21,22]. Familial forms of PD only account for 5%–10% of PD cases [23,24]. There are no clear reasons why the dopaminergic neurons die, but several molecular mechanisms have been pointed to be involved in PD pathology like mitochondrial dysfunction, proteostasis, lysosomal and autophagy failures, oxidative stress, and neuroinflammation [25–28].

Transgenic mouse models for the study of PD rely on the modeling of early-onset genetic forms of PD. Detailed information on all models listed below can be found at https://www.neurodegenerationresearch.eu. Surprisingly, introducing mutations known to cause PD in humans in mice only produces mild neurodegeneration and smooth phenotype (Table 1, Ref. [29–51]). Some models were proposed as useful to model early prodromal stages of PD due to their soft phenotypes characterized by mild functional impairments. However, a deep comparison of mutant *LRRK2-R1441G* mice as well as *DJ-1*, *PINK1*, and *PARK2* KO mice with wild-type controls did not detect differences in dopamine release [52]. It must be noted that other rodent models for PD study exist, relying on the use of neurotoxins like 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or aggregated α-syn injections to induce the loss of dopaminergic neurons in the substantia nigra.

2.1.1 Alpha-Synuclein (SNCA)

Mutations in the *SNCA* gene that cause genetic PD in humans are transmitted by autosomal dominant inheritance. To date, six disease-causing mutations have been identified: A30P, E46K, H50Q, G51D, A53T, and A53E, all located in the N-terminal region of the α-syn protein. In general terms, transgenic mouse lines for the *SNCA* gene show little loss of dopaminergic neurons but the aggregation of α-synuclein is more frequently found (Table 1). The development of motor and non-motor symptoms is also highly variable and model dependent. Given the variety of different promoters used and mutations modeled, the lack of a proper model seems to be related to intrinsic differences in how humans and mice dopaminergic neurons react to mutations in the *SNCA* gene. For instance, wild-type mice normally harbor a T in position 53 which in humans is associated with the genetic development of PD. In addition, the mice substrain C57B1/6OlaHsd naturally lack α-syn expression, being normal [53]. This phenomenon was also observed in transgenic mice genetically engineered to not express the *SNCA* gene [29–31], although one line exhibited abnormalities in synaptic morphology and function, along with fairly subtle behavioral changes [29].

2.1.2 Leucine-Rich Repeat Kinase 2 (LRRK2)

Mutations in the *LRRK2* gene that cause genetic PD in humans are transmitted by autosomal dominant inheritance and are the most prevalent genetic cause of PD. They are associated with PD classical clinical features and a late-onset of the disease. Only a few mutations have been linked to the disease (G2019S, R1441C, R1441G, R141H, I2020T, and Y1699C) but many others have been identified as risk factors (over 40 different mutations). *LRRK2* has been linked to various possible pathogenic mechanisms including α-syn and tau aggregation, inflammation, oxidative stress, and mitochondrial, synaptic, and autophagy-lysosomal dysfun-

Table 1. Transgenic mouse models of Parkinson's disease (PD).

Gene	Generation technique	Name	Promoter	Construct	Neuronal loss (substantia nigra)	α-syn protein deposition	Clinical signs	Reference
SNCA	Transgenic-Microinjection	*α-synuclein A30P/A53T* Mouse (Tg)	*Th* (rat)	*SNCA* (A30P/A53T)	Yes	No	Atrophic axons and dendrites in the dopaminergic system, reduced motor coordination	[32]
		α-synuclein A53T Mouse (Tg)	*Prnp*	*SNCA* (A53T)	No	Yes	Alterations in dopaminergic-associated proteins in some brain areas, accumulation of ubiquitin and neurofilament-H, astrocytosis, severe motor impairment, memory impairment, premature death	[33]
		Thy1-αSyn "Line 61" Mouse	*Thy1*	*SNCA*	No	Yes	None	[34]
	Transgenic-Knock out	*α-synuclein* KO Mouse	*Snca*	*Snca* interruption (neomycin)	No	No	Abnormal regulation in synaptic vesicle mobilization at nerve terminals	[29]
		α-synuclein KO Mouse (Conditional)	*Snca*	*Snca* interruption (Cre-LoxP system)	No	No	None	[30,31]
LRRK2	Transgenic-Microinjection	*LRRK2 G2019S* Mouse (BAC Tg)	*Lrrk2*	*Lrrk2* (G2019S)	No	No	Decreased striatal dopamine content, decreased evoked release	[35]
		LRRK2 G2019S Mouse (Tg)	*CMVe-PDGFβ*	*LRRK2* (G2019S)	Yes	No	Abnormal mitochondria in striatal neurons and microglia, activated microglia in striatum, anxiety/depression like behavior in middle age	[36]
		LRRK2 R1441C Mouse (Tg - Conditional)	*ROSA26 (conditional)*	*LRRK2* (R1441C)	No	No	Subtle morphological abnormalities in neuronal nuclei	[37]
		LRRK2 R1441G Mouse (BAC Tg)	*Lrrk2*	*LRRK2* (R1441G)	No	No	Age-dependent and levodopa-responsive slowness of movement associated with diminished dopamine release and axonal pathology of nigrostriatal dopaminergic projection	[38]

Table 1. Continued.

Gene	Generation technique	Name	Promoter	Construct	Neuronal loss (substantia nigra)	α-syn protein deposition	Clinical signs	Reference
DJ-1	*Transgenic-Knock out*	*DJ-1 Null Mice*	*Dj-1*	*Dj-1* first 5 exons and part of the promoter deletion	No	No	Age-dependent and task-dependent motoric behavioral deficits ,changes in striatal dopaminergic function	[39]
		DJ-1$^{-/-}$	*Dj-1*	*Dj-1* exon 2 replacement (neomycin)	No	No	Progressive behavioral changes without significant alterations in nigrostriatal dopaminergic and spinal motor systems	[40]
		DJ-1$^{-/-}$ *Mice*	*Dj-1*	*Dj-1* exon 2 replacement (neomycin)	No	No	Alterations in nigrostriatal dopaminergic and spinal motor systems	[41]
		DJ1-C57	*Dj-1*	*Dj-1* null mice backcrossed 14 times onto a pure C57BL/6J background	Yes	No	Aging-dependent bilateral degeneration of the nigrostriatal axis and nucleus ceruleus, mild motor behavior deficits	[42]
		DJ-1 KO Mice	*Dj-1*	*Dj-1* exon 2-3 replacement (neomycin)	No	No	The mice are anatomically and behaviorally similar to WT mice	[43]
		DJ-1$^{-/-}$	*Dj-1*	*Dj-1* exon 3-5 replacement (neomycin)	No	No	The mice are anatomically and behaviorally similar to WT mice	[44]
PINK1	Transgenic-Knock in	*PINK1 G309D (PINK1*$^{-/-}$*)* Mouse (KI)	*Pink1*	*Pink1* (G309D)	No	No	Mitochondrial dysfunction, electrophysiological abnormalities, subtle alterations in gene expression in brain areas	[45]
	Transgenic-Knock out	*PINK1* KO Mouse	*Pink1*	*Pink1* interruption (PGK-Neo)	No	No	Heavier than wildtype mice at 5 months, subtle plasticity abnormalities	[46]
PARK2	Transgenic-Knock out	*Parkin*$^{-/-}$ Mice	*Park2*	*Park2* exon 3 replacement (EGF-PGK-neo)	No	No	Reduction in synaptic excitability, deficits in behavioral paradigms sensitive to dysfunction of the nigrostriatal pathway	[47]
		Parkin mutant mice	*Park2*	*Park2* exon 3 and intron 4 replacement (neomycin)	No	No	Motor and cognitive deficits, inhibition of amphetamine-induced dopamine release and inhibition of glutamate neurotransmission	[48,49]
		Parkin Null Mice	*Park2*	*Park 2* exon 7 deletion (Cre-LoxP system)	No	No	Loss of catecholaminergic neurons in the locus coeruleus, loss of norepinephrine in discrete regions of the brain	[50]
DJ-1, PINK1, PARK2	Transgenic-Knock out	*TKO* mice	*Dj-1/Pink1/Park2*	Crossing of *DJ-1*$^{-/-}$ Mice, *PINK1* KO Mouse and *Parkin*$^{-/-}$ Mice	No	No	Levels of striatal dopamine increased at 24 months	[51]

ctions [54]. None of the transgenic lines generated for the *LRRK2*-associated PD recapitulates the human PD phenotype, regardless of the mutation modeled (Table 1). Relatively successful models achieved α-syn aggregation and development of motor symptoms but no neurodegeneration or neurodegeneration plus motor symptoms and no α-syn aggregation.

2.1.3 Protein Deglycase DJ-1 (DJ-1)

Mutations in *DJ-1* have been identified in autosomal recessive forms of early-onset PD. These mutations involve loss of function missense mutations and large deletions [55]. KO mice for the *DJ-1* gene do not recapitulate the human PD phenotype (Table 1). No clear motor symptoms, α-syn aggregation, and neuron loss have been detected [39,40] but subtle dysfunctions have been reported in a few models [39–42]. However, *DJ-1* KO mice have been useful to study the role of the DJ-1 protein, which has been related to mitochondrial function [43,44].

2.1.4 Phosphatase and Tensin Homolog (PTEN)-Induced Kinase 1 (PINK1)

Recessive mutations in the *PINK1* gene cause early-onset PD being the second-commonest cause of autosomal recessive early-onset PD. KO mice for the *PINK1* gene did not develop a ND but show impaired mitochondrial and neuronal function [45,46,56,57]. The most important models are included in Table 1.

2.1.5 Parkin (PARK2)

The *PARK2* gene, coding for the Parkin or ubiquitin E3 ligase protein, was the first gene associated with autosomal recessive PD. More than fifty different mutations in the *PARK2* gene cause PD. As mentioned above, with other genes, *PARK2* KO in mice did not produce a clear PD phenotype. Models just showed partial and mild signs of PD like deficits in the dopamine system and motor symptoms, but none or only moderate loss of dopaminergic neurons was detected [47–50,58]. However, noradrenergic neurons in the locus coeruleus were found to degenerate in other *PARK2* KO models [59]. The most important models are included in Table 1.

2.1.6 Combined Models

Since Parkin, PINK1, and DJ-1 proteins conform to a ubiquitin E3 ligase protein complex, a triple KO mouse lacking expression of the three genes was generated (Table 1). Unfortunately, this complex model did not present neuron degeneration [51].

2.2 Multiple System Atrophy (MSA)

MSA is rarer than the other synucleinopathies [60] and is clinically divided into two subtypes based on different phenotypes, parkinsonian MSA or MSA-P (associated with the loss of nigrostriatal dopaminergic neurons) and cerebellar MSA or MSA-C (associated with the loss of olivopontocerebellar neurons). While MSA-P patients show more typical PD symptoms, MSA-C patients develop cerebellar ataxia. PD and MSA are clinically quite similar and although differential diagnosis based on clinical symptoms is possible, neuropathological confirmation is necessary for a definitive MSA diagnosis. In MSA pathology, oligodendrocytes play the main role due to the presence of α-syn intracytoplasmic inclusions named glial cytoplasmic inclusions (GCI) which are used as main the neuropathological hallmark for MSA diagnosis [61]. GCIs are spherical protein aggregates composed mainly of phosphorylated α-syn.

As mentioned before for PD, there are MSA models that rely on neurotoxins to induce the loss of dopaminergic neurons in the substantia nigra. Apart from 6-OHDA and MPTP, quinolinic acid, 3-nitropropionic acid (3-NP) and 1-methyl-4-phenylpyridinium ion (MPP+) can be used to produce pathology in the nigrostriatal system [62–69]. Nevertheless, it must be noted that the generated pathology does not transmit outside the basal ganglia and does not induce the formation of GCIs [70].

Transgenic mouse models for the study of MSA have been generated by driving mutated or wild-type α-syn expression to oligodendrocytes using specific promoters. In general lines, transgenic mouse lines that overexpress α-syn in their oligodendrocytes show motor and non-motor symptoms as well as oligodendroglial α-syn aggregates resembling human GCIs (Table 2, Ref. [71–78]). Interestingly, promoter election for the transgenic generation seems to impact the phenotypes shown by the different transgenic lines and none of them fully replicate the two differentiated human MSA phenotypes.

3. Transgenic Mouse Models for the Study of Non-Alzheimer Tauopathies

Tauopathies are NDs characterized by the pathological accumulation of microtubule-associated protein tau (MAPT) in neurofibrillary tangles (NFTs) and paired helical filaments (PHFs) that cause the death of affected neurons and glial cells. Tauopathies include frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), corticobasal degeneration syndrome (CBS), chronic traumatic encephalopathy (CTE), Pick's disease, and sporadic forms of AD. Some of them are inherited by mutations in the *MAPT* gene [79–93]. Given that AD has other molecular hallmarks and is the most common form of ND, the models for its study will address separately, being this part focused on other non-Alzheimer tauopathies.

MAPT is a neuronal protein involved in the regulation of microtubule stability, microtubule dynamics, and axonal transport [94,95]. Many *MAPT* mutations cause the inheritance of genetic forms of tauopathies supposedly by increasing tau's propensity for aggregation and toxicity [96]. Nevertheless, as reported with other NDs, the majority of tauopathies are sporadic, and variable clinical

Table 2. Transgenic mouse models of multiple system atrophy (MSA).

Gene	Generation technique	Name	Promoter	Construct	Dopaminergic neuron loss	α-syn protein deposition	Clinical signs	Reference
SNCA	Transgenic-Microinjection	*PLP-αsyn*	*PLP*	*SNCA*	Yes	Yes	Ser_{129} α-syn phosphorylation, GCI-like inclusions, gliosis, cytokine production, motor symptoms, autonomic symptoms	[71–75]
		MBP29-hα-syn	*MBP*	*SNCA*	Yes	Yes	Ser_{129} α-syn phosphorylation, GCI-like inclusions, astrogliosis, neuroinflammation, cytokine production, demyelination, motor symptoms, behavioral symptoms, premature death of a higher expressor line	[76,77]
		M2 mice	*CNP*	*SNCA*	Yes	Yes	Ser_{129} α-syn phosphorylation, GCI-like inclusions, gliosis, demyelination, motor symptoms	[78]

and pathological presentations have been described in patients [79]. The mechanisms of tau aggregation as well as the disruption of molecular pathways that ultimately cause cell death are still poorly understood. Evidence indicates that native tau is soluble, contains charged and hydrophilic residues, and shows little tendency for aggregation [97–99]. Thus, to aggregate, tau must undergo conformational and post-translational modifications like phosphorylation [100–103]. It has been reported that phosphorylation at certain residues like Ser422 is rarely detected in healthy adults [104] but is present in AD patients and related to loss of cholinergic neurons and cognitive impairment [105,106].

Frontotemporal Dementia (FTD)

Several related disorders are included in the spectrum of FTD. Among the different clinical diagnoses, the most common one is behavioral variant FTD (bvFTD) [107]. Even in the category of bvFTD, pathological heterogeneity is a common phenomenon, since several misfolded proteins have been found to aggregate and cause frontotemporal lobar degeneration in patients. One of these misfolded proteins is tau. The neuropathological term for cases with tau pathology is Frontotemporal lobar degeneration (FTLD)-tau and the clinical term for cases with *MAPT* mutations in frontotemporal dementia and parkinsonism linked to chromosome 17, tau gene (FTDP-17T). Patients with *MAPT* mutations thus present FTLD-tau pathology and are likely to have the same clinical syndromes associated with sporadic FTLD-tau [108]. Given these strong associations between both etiologies, transgenic mouse models for the study of FTLD-tau rely on modeling the genetic forms caused by *MAPT* mutations.

More than 40 different *MAPT* mutations have been associated with FTDP-17T [109]. Most of them are missense mutations located in the microtubule-binding region or other regions of the protein. However, mutations in such other regions are thought to end structurally and functionally related to the microtubule-binding domain due to protein folding [110]. Tau mutations have been attributed to causing both loss-of-function and gain-of-function effects by reducing microtubule stabilization and increasing its aggregation and phosphorylation respectively [111,112].

Detailed information on all models listed below can be found at https://www.alzforum.org/. The most important transgenic lines used for FTDP-17T modeling can be found in Table 3 (Ref. [113–134]). Transgenic mice devoid of tau expression resulted in no overt phenotype or malformations, although age-associated behavioral changes and subtle motor deficits have been identified in certain lines [135]. Nevertheless, these lines were fundamental to identifying tau functions (reviewed in [135]). On the other hand, transgenic mice expressing wild-type human tau also remain unaffected except for the Tg2652 transgenic line [113] in which human tau is greatly overexpressed producing widespread pretangle pathology at a young age, but the phenotype does not progress to mature neurofibrillary tangles or neuronal loss [113]. Behaviorally, these mice show deficits in muscle strength, as well as in spatial learning and memory [113]. The most useful models rely on the expression of human tau harboring *MAPT* mutations like P301S and P301L (Table 3). In human-mutated MAPT models, the expression of mutant tau was sufficient to cause tau aggregation in NFTs and neuronal death. Indeed, in certain models both processes could be dissociated, suggesting that soluble tau aggregates are responsible for neuronal death instead of the larger NFTs [114–117]. Functional deficits like synaptic loss, behavioral changes, and cognitive impairment have also been reported in human mutated tau models and proved to be reversible in conditional transgenic lines [117–119,136].

Table 3. Transgenic mouse models of frontotemporal dementia (FTDP-17T).

Gene	Generation technique	Name	Promoter	Construct	Neuronal loss	Tau protein deposition	Clinical signs	Reference
MAPT	Transgenic-Microinjection	*JNPL3*	*Prnp*	*MAPT* (P301L)	No	Yes	NFTs, gliosis, motor symptoms, behavioural symptoms	[120]
		rTg4510	*CaMKIIα* (Tet-off)	*MAPT* (P301L)	Yes	Yes	NFTs, memory deficits, cognitive impairment	[115,116,121]
		PS19	*Prnp*	*MAPT* (P301S)	Yes	Yes	NFTs, microglial activation, synaptic plasticity deficits	[118]
		Pro-Aggr	*CaMKIIα* (Tet-off)	*MAPT* (ΔK280)	Yes	Yes	NFTs, astrogliosis Missorting, phosphorylation, and aggregation of TauRD/ΔK280 protein are reversible after switching off the expression, only mouse Tau tangles tend to persist	[117,119]
		Anti-Agrr	*CaMKIIα* (Tet-off)	*MAPT* (ΔK280, I277P, I308P)	No	No	None (I227P and I308P mutations inhibit Tau aggregation *in vitro* and in cell models)	[117]
		pR5	*Thy1.2*	*MAPT* (P301L)	Yes	Yes	Astrocytosis, NFTs	[122]
		hTau	*MAPT*	Genomic *MAPT* or cDNA *MAPT*	No	Yes	Tau-immunoreactive axonal swellings and aggregation, hind-limb abnormality	[114,123,124]
		hTau-A152T	*CaMKIIα* (Tet-off)	*MAPT* (A152T)	Yes	Yes	Abnormal accumulation of soluble Tau, learning and memory deficits	[125]
		hTau.P301S	*Thy-1*	*MAPT* (P301S)	Yes	Yes	NFTs, astrocytosis, motor deficits	[126]
		mThy-1 3R Tau	*Thy-1*	*MAPT* (L266V, G272V)	Yes	Yes	Pick-body type Tau aggregates, astrogliosis, mitochondrial patology, memory deficits, motor deficits, increased anxiety	[127]
		Tau4RTg2652	*Thy1.2*	*MAPT*	No	-	Tau hyperphosphorylation, neuron dystrophy, motor deficits, cognitive deficits	[113]
	Transgenic-Knock in	*hTau-AT*	*Thy1.2*	*MAPT* (A152T)	Yes	Yes	NFTs, learning and memory deficits	[128,129]
	Transgenic-Knock out	*tau*$^{-/-}$ mice	*Mapt*	*Mapt interruption* (neomycin)	No	No	None at young age, subtle motor deficits at 1 year of age	[130,131]
		TAU$^{-/-}$ mice	*Mapt*	*Mapt interruption* (neomycin)	No	No	None at young age, complex motor deficits at elder age, slower neuron maturation	[132,133]
		tau knockout mice	*Mapt*	*Mapt interruption* (neomycin)	No	No	None	[134]

4. Transgenic Mouse Models for the Study of Alzheimer's Disease

AD is the most prevalent form of dementia and contributes to 60–70% of all dementia cases [137]. Patients show progressive symptoms that firstly include deficits in short-term memory that led to later cognitive impairment and neuropsychiatric symptoms that severely disable patients to the extent of being unable normal life activities [138].

AD is mainly characterized by the presence in diseased brains of amyloid plaques composed of amyloid-β (Aβ) peptides derived from the processing of the amyloid precursor protein (APP) and NFTs composed of hyperphosphorylated tau [139]. Such hallmarks were first reported in 1906 by German doctor Alois Alzheimer [140]. Apart from amyloid plaques and NFTs, AD brains are further characterized by synaptic and neuronal loss and reactive astrogliosis and microgliosis [141].

The discovery that amyloid plaques were composed of Aβ peptides pointed to Aβ as being the potential causal factor for AD. Aβ peptides are formed during the cleaving of the transmembrane APP protein by proteases BACE1 [142] and gamma-secretase complex, releasing peptides Aβ40 and Aβ42 to the extracellular space [143]. These peptides are extremely hydrophobic and prone to aggregate, forming insoluble fibrils which turn into plaques. Initially, Aβ deposits were thought to be neurotoxic and promote the formation of NFTs by a similar cascade of polymerization of phosphorylated tau molecules into progressively bigger and insoluble fibrils that end up forming NFTs [144,145]. However, cumulative evidence showed that AD has a more complex and multifactorial pathogenesis, in which cognitive decline seems to be more linked to NFTs accumulation than to Aβ deposition [146]. In addition, it seems that soluble Aβ and tau oligomers that precede amyloid plaque and NFTs are the causative agents of synaptic damage and neuronal death [147–149].

More than 90% of AD cases are late-onset and of unknown etiology, which are known as sporadic AD cases (SAD) [150]. By contrast, the rest of the AD cases are caused by dominant autosomal inheritance of mutations in genes related to Aβ generation like *APP*, *PSEN1*, and *PSEN2*. These last two genes codify proteins acting in the gamma-secretase complex. The familial forms of AD (FAD) are early-onset and high penetrant. Transgenic mouse modeling FAD aimed to gain insights into molecular mechanisms that will later be applied to SAD cases. However, there is no single mouse model that completely recapitulates all pathological and behavioral phenotypes of AD. Indeed, wild-type rodents do not develop Aβ plaques or NFTs in normal conditions possibly because of their lifespan, which may not allow a long pre-symptomatic phase as happens in humans [151]. The most relevant transgenic mouse models generated to model AD will be discussed and their main advantages and caveats analyzed (Table 4, Ref. [144,152–174]). It is important to note that before FAD modeling, models aimed to mimic the disruption in the cholinergic system in rodents by mechanical, electrical, or chemical lesions [175]. More detailed information about the AD transgenic mouse models available can be found at https://www.alzforum.org/.

4.1 Amyloid-Beta Precursor Protein (APP)

AD senile plaques are mainly composed of Aβ peptides that result from the proteolytic processing of the APP protein. The discovery of FAD linked to point mutations in the *APP* gene led to the development of many transgenic mouse models based on *APP* genetic modification (Table 4). Point mutations causative of FAD is mainly amino acid substitutions that received the names of the populations in which they were discovered (for instance, the E693Q or so-called Dutch mutation). Mutations in APP are also associated with cerebral amyloid angiopathy disease [176].

The disruption of the *APP* gene to generate KO mice resulted in animals that do not show physical symptoms, although some subtle phenotypes including behavioral deficits were described [177]. In the same line of results microinjected, knock-in, and CRISP/CAS9 transgenic mice produced to express wild-type human APP protein showed in general terms no neuropathology, behavior, or cognitive phenotypes although some subtle phenotypes were also reported (Table 4).

By contrast, the vast majority of models expressing the human *APP* gene harboring mutations related to FAD end developing amyloid plaques at different points of their lifespan as well as memory and cognitive deficits as measured by different performing tests like the Morris water maze test [138]. However, neuropathological findings were exclusive to Aβ deposits, even in cases in which more than one *APP*-FAD-linked mutation was introduced in the *APP* sequence. Some models presented abnormal tau phosphorylation as well [152,153] but overt NFT pathology was not achieved.

4.2 Presenilin-1 (PSEN1)

PSEN1 encodes presenilin-1, one of the four subunits of the gamma-secretase complex responsible for Aβ generation. More than 300 mutations in *PSEN1* have been reported, and mutations in *PSEN1* are the most common cause of early-onset Alzheimer's disease [163].

Inactivation of the *PSEN1* gene led to negative phenotypes including impaired neurogenesis and neuron maturation, massive neuronal loss, brain hemorrhages, behavior deficits, and premature death as well as abnormalities in Aβ processing [178]. By contrast, expression of the human wild-type *PSEN1* produced no pathological changes [163].

The introduction of FAD-linked mutations in the *PSEN1* sequence did not produce overt Aβ deposition, although certain dysregulations in normal APP processing

were detected (Table 4). Other detected phenotypes included altered mitochondrial activity, dysregulated calcium homeostasis, and increased sensitivity towards kainic acid in terms of seizures and neuronal damage. Irrespective of the mutation modeled, a proper AD phenotype was not achieved in *PSEN1* transgenic mice.

4.3 Presenilin-2 (PSEN2)

The gene *PSEN2* encodes presenilin-2, another subunit of the gamma-secretase complex involved in *APP* processing and Aβ generation. Missense mutations in *PSEN2* are a rare cause of early-onset Alzheimer's disease [178].

Disruption of the *PSEN2* gene in transgenic mice did not produce brain, cognitive or behavioral abnormalities, although the function of the mice's respiratory system was compromised [169]. Transgenic mice expressing the FAD-linked mutation N141I did also not present any AD-related histological finding, although behavioral deficits, alterations in normal APP processing, and impaired calcium homeostasis were reported (Table 4).

4.4 Combinatorial Models

Since transgenic mice for *APP*, *PSEN1*, and *PSEN2* genes did not faithfully reproduce the AD phenotype, combinatorial models harboring mutations in more than one gene linked to FAD have been generated (Table 4). Mutations in the *MAPT* gene were also included in some of the models given that solid tau pathology was not achieved by solely altering APP processing involved genes. These models were produced either by crossing previously existing single-gene transgenic mice or by delivering the desired transgenes all at once.

In general terms, combinatorial models are more successful in reproducing certain FAD hallmarks (Table 4). Aβ deposits appear earlier, in more amounts, are better organized in amyloid plaques, and tend to extend more through different brain areas. In addition, amyloid plaques were even surrounded by dystrophic neurons and activated microglia and astrocytes. Neuronal loss was detected in some models. Tau pathology is also detected in that models in which the *MAPT* gene was also mutated, although in some models proper NFT formation was not achieved. FAD combinatorial models also show cognitive impairment that worsens with age and is mainly focused on memory tasks. Motor phenotypes were also reported in certain models.

Although combinatorial models produced invaluable insights into FAD-related mechanisms, it is important to note that they do not fully reproduce human AD phenotype. In addition, the combination of mutations in several genes, even with more than one mutation in one single gene which is used to generate the combinatorial models, does not exist in humans.

5. Transgenic Mouse Models for the Study of Huntington's Disease

Huntington's disease (HD) is an inherited ND mainly characterized by motor, psychiatric and cognitive impairments [179]. Unstable CAG repeat expansion in the huntingtin gene (*HTT*) is the cause of the disease, which codifies for a polyglutamine domain in the N-terminal part of the protein. HD is inherited in an autosomal dominant pattern. Healthy *HTT* alleles contain from 6 to 35 repeats of the CAG triplet in the $(CAG)_nCAACAG$ region of the *HTT* gene. A higher risk of disease development has been established from 36 to 39 repeats, while 40 or more repeats cause fully penetrant HD. The age of onset of motor symptoms negatively correlates with the CAG repeat number, the more repeats the sooner the symptoms appear. The main pathological hallmark of HD is the extended neuronal loss in the striatum and cerebral cortex areas as well as extensive brain atrophy [180].

Once the *HTT* gene was discovered in 1993 [181] a great variety of HD animal models have been produced including transgenic mice. These models have been of utility for unraveling the pathological mechanisms of the disease and for the evaluation of therapeutic interventions in preclinical studies (Table 5, Ref. [182–195]).

HTT gene ablation in mice results in early embryonic lethality. Thus, the normal function of huntingtin in adult mice relies on the Cre/loxP site-specific recombination strategy to produce conditional ablation, finally resulting in a progressive degenerative neuronal phenotype [182]. In contrast with the experience of other NDs, *HTT* transgenic mice do recapitulate human HD phenotype including brain HTT aggregates and inclusions, motor and cognitive impairment, synaptic plasticity deficits, electrophysiological alterations, and neuron loss (Table 5). Motor symptoms include tremors, hypokinesia, and lack of coordination. Interestingly, transgenic mice expressing only the mutant N-terminal part of the *HTT* gene codifying only for exon 1 develop the disease earlier and with more pronounced symptoms than transgenic mice expressing several copies of the full mutant *HTT* gene or knock-in mice [183–186]. Despite this disadvantage of full-length *HTT* models, they are more suitable for the study of certain *HTT* therapeutic interventions like *HTT* lowering strategies [187–190].

6. Transgenic Mouse Models for the Study of Prion Diseases

Transmissible spongiform encephalopathies (TSEs) or prion diseases are fatal neurodegenerative diseases that affect humans and other mammal species, some of them included in the human food chain. Humans are affected by Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), and familial fatal insomnia (FFI). TSEs produce long incubation times and their main symptoms are neurological behavior abnormalities,

Table 4. Transgenic mouse models of Alzheimer's disease (AD).

Gene	Generation technique	Name	Promoter	Construct	Neuronal loss	Aβ deposition	Clinical signs	Reference
APP	Transgenic-Microinjection	*A7 APP* transgenic	*Thy1.2*	*APP* (K670M, N671L, T714I)	-	Yes	Optogenetic stimulation, induced epileptic seizures	[154]
		APP23	*Thy 1*	*APP* (K670M, N671L)	Yes	Yes	Microglia activation, dystrophic neurites containing hyperphosphorylated Tau, memory deficits, hyperactivity	[152]
		APPDutch	*Thy 1*	*APP* (E693Q)	-	Yes	Aβ deposition in blood vessels, gliosis	[155]
		APP E693Δ-Tg (Osaka)	*Prnp*	*APP* (E693Δ)	Yes	Yes	Aβ deposition, dystrophic neurites, abnormal Tau phosphorylation, gliosis, cognitive impairment	[153]
		APPSwe	*Thy1.2*	*APP* (K670M, N671L)	-	Yes	Aβ plaques	[156]
		J20	*PDGF-β*	*APP* (K670M, N671L, V717F)	Yes	Yes	Aβ plaques, dystrophic neurites, learning deficits, memory deficits, hiperactivity	[157]
		Tg2576	*Prnp* (hamster)	*APP* (K670M, N671L)	No	Yes	Aβ plaques, vascular amyloid, astrogliosis, microgliosis, cognitive impairment	[158]
		TgCRND8	*Prnp* (hamster)	*APP* (K670M, N671L, V717F)	Yes	Yes	Aβ plaques, activated microglia, dystrophic neurites, cognitive impairment, cholinergic dysfunction	[159]
	Transgenic-Knock in	*APP NL-F* Knock-in	*App*	*App* (K670M, N671L, I716F)	No	Yes	Aβ plaques, microgliosis, astrocytosis, synaptic loss, memory impairment	[160]
		APP NL-G-F Knock-in	*App*	*App* (K670M, N671L, I716F, E693G)	No	Yes	Aβ plaques, microgliosis, astrocytosis, synaptic loss, memory impairment	[160]
		App knock-in (humanized Aβ)	*App*	*APP*	No	No	None	[161]
		hAβ-KI	*App*	*APP*	No	No	None	[162]
	Transgenic-Knock out	*APP*-Deficient mice	*App*	*App* interruption (neomycin)	No	No	Lower weight, decreased locomotor activity and forelimb grip strength, reactive gliosis at 14 weeks of age	[144]
PSEN1	Transgenic-Microinjection	*PSEN1(WT)*	*Nse*	*PSEN1*	No	No	None	[163]
		PS1(A246E)	*Thy 1*	*PSEN1* (A246E)	No	No	None	[165]
		PS1(M146L)	*Pdgf-β* (rat)	*PSEN1* (M146L)	No	No	Disregulation of calcium homeostasis	[166]
		PS1(M146V)	*Pdgf-β* (rat)	*PSEN1* (M146V)	No	No	Disregulation of calcium homeostasis	[166]
	Transgenic-Knock in	*PS1(P264L)*	*Psen1*	*Psen1* (P264L)	No	No	None	[167]
		PSEN1(M146V) Knock-In	*Psen1*	*Psen1* (M146V)	No	No	Disregulation of calcium homeostasis	[168]
	Transgenic-Knock out	*PS1* Null mice	*Psen 1*	*Psen 1 interruption* (neomycin)	Yes	No	Limited survival. Skeleton deformation, CNS hemorrhages, neurogenesis impairment, massive neuronal loss in specific subregions	[164]

Table 4. Continued.

Gene	Generation technique	Name	Promoter	Construct	Neuronal loss	Aβ deposition	Clinical signs	Reference
PSEN2	Transgenic-Microinjection	*NSE-hPS2(N141I)*	*Nse*	*PSEN2* (N141I)	No	No	None	[170]
		PS2(N141I)	*Prnp*	*PSEN2* (N141I)	No	No	Disregulation of calcium homeostasis	[156]
	Transgenic-Knock out	*PS2*-Deficient Mice	*Psen 2*	*Psen 2 interruption* (hygromycin)	No	No	Mild pulmonary fibrosis and pulmonary hemorrhage	[169]
APP/PSEN1	Transgenic-Microinjection	*5xFAD*	*Thy 1*	*APP* (K670M, N671L, I716V, V717I)/*PSEN1* (M146V, L286V)	Yes	Yes	Aβ plaques, gliosis, synaptic dysfunction, cognitive impairment, motor symptoms	[170]
		APPPS1	*Thy 1*	*APP* (K670M, N671L)/*PSEN1* (L166P)	No	Yes	Aβ plaques, gliosis, synaptic dysfunction, cognitive impairment	[171]
		APPPS1	*Thy 1*	*APP* (K670M, N671L)/*PSEN1* (L166P)	Yes	Yes	Aβ plaques, gliosis, synaptic dysfunction, cognitive impairment	[172]
APP/PSEN2		*PS2APP*	*Thy1.2 (APP)/Prnp (PSEN2)*	*APP* (K670M, N671L)/*PSEN2* (N141I)	No	Yes	Aβ plaques, gliosis, synaptic dysfunction, cognitive impairment, dysregulation of calcium homeostasis	[173]
APP/PSEN1/MAPT		*3xTg*	*Thy1.2*	*APP* (K670M, N671L)/*PSEN1* (M146V)/*MAPT* (P301L)	Yes	Yes	Aβ plaques, NFTs, synaptic dysfunction, cognitive impairment	[174]

Table 5. Transgenic mouse models of Huntington's disease (HD).

Gene	Type of HD model	Generation technique	Name	CAG repeat lenght	Promoter	Construct	Striatum neuron loss	Huntingtin protein deposition	Clinical signs	Reference
HTT	N-terminal transgenic and fragment models	Transgenic-Microinjection	*R6/1*	116	*HTT*	Exon 1 *HTT* containing genomic fragment	Yes	Yes	Motor and cognitive impairment, failure to gain weight	[183]
			R6/2	116 128 160 168 251 293	*HTT*	Exon 1 *HTT* containing genomic fragment	Yes	Yes	Dossage effect on age of onset and phenotype severity Motor and cognitive impairment, failure to gain weight, deficits in synaptic plasticity, cardiac and skeletal muscle abnormalities	[184]
			N171-82Q	82	*Prnp*	First 171 amino acids *HTT*	No	Yes	Motor and cognitive impairment, failure to gain weight	[185]
			Tg100	100	*NSE* (rat)	First 3 kb of *HTT* cDNA	No	Yes	Motor and cognitive impairment, abnormal dendritic morphology, failure to gain weight	[186]

Table 5. Continued.

Gene	Type of HD model	Generation technique	Name	CAG repeat lenght	Promoter	Construct	Striatum neuron loss	Huntingtin protein deposition	Clinical signs	Reference
HTT	Transgenic full-lenght models	Transgenic-Bacterial artificial chromosome	*BACHD*	97	*HTT*	Exon 1 *HTT*	No	Yes	Motor and cognitive impairment, abnormal striatal morphology, weight gain	[187]
		Transgenic-Yeast artificial chromosome	*YAC128*	125	*HTT*	*HTT*	Yes	Yes	Motor and cognitive impairment, weight gain	[188]
		Cross of BACHD and YAC18 mice	*Hu97/18*	18 and 97	*HTT*	Exon 1 *HTT*	No	Yes	Motor and cognitive impairment, striatal atrophy, weight gain	[189]
		Cross of YAC128 and BAC21 mice	*Hu128/21*	125 and 21	*HTT*	Exon 1 *HTT*	No	Yes	Motor and cognitive impairment, striatal atrophy, weight gain, testicular atrophy	[190]
		Transgenic-Knock in	*CAG140*	146	*Htt*	Chimeric *HTT* exon 1/*Htt*	No	Yes	Mild motor and cognitive impairment	[191]
			zQ175	188	*Htt*		No	-	Spontaneous expansion of the CAG copy number in CAG140 mice Motor and cognitive impairment, transcriptional dysfunction of striatal genes, failure to gain weight	[192]
			HdhQ20 *HdhQ50* *HdhQ80* *HdhQ92* *HdhQ111*	20 50 80 92 111	*Htt*		Not analyzed	Yes	Inherited instability of CAG repeats by gametogenesis	[193]
			HdhQ50 *HdhQ100* *HdhQ200* *HdhQ250* *HdhQ315* *HdhQ365*	50 100 200 250 315 365	*Htt*		No	Yes	Dossage effect on age of onset and phenotype severity Motor and cognitive impairment, reactive gliosis	[194]
			HdhQ150	150	*Htt*		No	Yes	Motor and cognitive impairment, transcriptional dysfunction of striatal and cerebellum genes, failure to gain weight	[195]
	Transgenic-Knock out		*R1ag5 L7ag13*	-	*Htt*	*Htt* interruption (Cre-LoxP system)	Yes	Yes	Progressive degenerative neuronal phenotype and sterility	[182]

Table 6. Transgenic mouse models of prion diseases.

Gene	Prion disease	Mutation	PrP sequence	Generation technique	Name	Spontaneous disease (onset)	Neuropathology	PrP^{res}	Transmissibility	Reference
PRNP	None	*Prnp* interruption (neomycin)	Mouse	Transgenic-Knock out	*Zurich I*	No	No	No	-	[203]
		Prnp interruption (neomycin)	Mouse		*Npu*	No	No	No	-	[204]
		Prnp interruption (TALEN-mediated genome editing)	Mouse		*Zurich III*	No	No	No	-	[207]
		None (Wt)	Human V129	Transgenic-microinjection	*Tg152*	No	No	No	No	[208]
					Tg361	No	No	No	No	[209]
				Transgenic-Knock in	*HuVTg*	No	No	No	No	[210]
			Human M129	Transgenic-microinjection	*Tg440*	No	No	No	No	[208]
					Tg35	No	No	No	No	[211]
					Tg340	No	No	No	No	[212]
					Tg650	No	No	No	No	[213]
				Transgenic-Knock in	*HuMTg*	No	No	No	No	[210]
	fCJD	E200K	Human M129	Transgenic-microinjection	*Tg23*	No	No	No	-	[214]
			Bank vole I109		*Tg7271*	Yes (~120 d)	Yes	Yes	Yes	[215]
		D178N/V129	Mouse		*CJD-A21*	Yes (~150 d)	Yes	No	No	[216]
	GSS	P102L	Mouse		*Tg174*	Yes (~200 d)	Yes	No	Yes	[217]
					Tg87	Yes (~150 d)	Yes	No	Yes	[218]
					Tg2866	Yes (~150 d)	Yes	No	Yes	[219]
					Tg(GSS)22	Yes (~160 d)	Yes	No	Yes	[220]
			Cow		*113LBoPrP-Tg037*	Yes (~190 d)	Yes	No	Yes	[221]
			Human M129		*Tg27*	No	No	No	-	[217]
			Mouse	Transgenic-Knock in	*101LL*	No	No	No	-	[222]
		A117V	Mouse MV128	Transgenic-microinjection	*Tg(A116V)*	Yes (~150 d)	Yes	No	-	[223]
			Human V129		*Tg30*	Yes (~475 d)	Yes	No	Yes	[224]
	FFI	D178N/M129	Mouse		*FFI-26*	Yes (~200 d)	Yes	No	No	[225]
			Bank vole I109		*Tg15965*	Yes (~180 d)	Yes	Yes	Yes	[215]

PrP^{res}, Proteinase K-resistant PrP^{Sc}; Wt, Wild-type; d, days.

but motor dysfunction, cognitive impairment, and cerebral ataxia can also appear. In individuals affected by a TSE the normal form of the prion protein, also known as cellular form or PrP^{C}, is converted into a disease-associated form known as PrP^{Sc} [196]. PrP^{C} transformation into PrP^{Sc} causes a change in the protein tridimensional structure characterized by an increase in the β-sheet content [197]. While PrP^{C} is monomeric, soluble in nonionic detergents, and sensitive to protease action, PrP^{Sc} tends to aggregate, is not soluble in non-ionic detergents, and is partially resistant to proteases [198].

One of the main differences between prion diseases with the rest of NDs is that they have a wider range of different etiologies. They can be infectious, iatrogenic, sporadic, or genetic.

Infectious and iatrogenic prion diseases are caused by the entry of an external PrP^{Sc} source that starts transforming host PrP^{C} into new, ascent PrP^{Sc}. Thus, variant CJD (vCJD) is an infectious TSE caused by the consumption of Bovine Spongiform Encephalopathy (BSE)-contaminated meat products while iatrogenic CJD, for example, may be caused by a cornea transplant from a CJD-infected donor [199]. In the particular case of infectious TSEs, certain prion agents can be transmitted from one species to a different one. This is known as interspecies prion transmission and is affected by the homology between the primary sequences of inoculum PrP^{Sc} and host PrP^{C} [200]. Mismatches between sequences also influence TSE progression [200]. Thus, the study of prion transmission is of crucial importance from the point of view of human health and food safety. For that purpose, transgenic mouse lines expressing the prion protein from different species of interest would provide useful models for the study of how certain TSEs may jump from one species to another.

Genetic TSEs are due to mutations in the *PRNP* gene. In humans, approximately 10–15% of TSEs are genetic [201]. *PRNP* mutations are thought to spontaneously promote the misfolding of PrP^{C} into PrP^{Sc} and/or stabilize the PrP^{Sc} molecules once formed [201]. There are three different human genetic prion diseases based on their clinical and pathological features: familial CJD (fCJD), GSS, and FFI [202]. fCJD is rapidly progressive dementia in which patients present cerebral spongiform degeneration. GSS is a slowly progressive disease in which patients show ataxia, few spongiform degeneration, and abundant PrP^{Sc} amyloid plaques. Finally, the principal FFI symptom is progressive insomnia that derives in hallucinations and dementia, as well as high spongiosis in the thalamus.

The prion protein amino acid sequence is well conserved throughout evolution in mammal species [202]. This fact suggests that the prion protein in its cellular form has an important function. However, KO mice for the *PRNP* gene were fully developed till the end of their lifespan without any obvious detriment phenotypes [203,204]. Different functions were inferred for the prion protein, but there is controversy on which of these inferred functions are real and the role that the different genetic backgrounds of the animal models may have played in the observed phenotypes [205] like synaptic and electrophysiological deficits, hematopoietic stem cell renewal, circadian rhythm regulation, processing of sensory information in the olfactory system or neural stem cell proliferation in adult neurogenesis [203,204]. However, the most important and validated effect of *PRNP* depletion is resistance to prion infection [203,204,206].

With a focus on human health, transgenic mice expressing human PrP have been developed to study genetic, sporadic, and infectious prion diseases (Table 6, Ref. [203,204,207–225]). Different human PrP transgenic lines have been produced and found susceptible to kuru and sCJD prions [208–211,226,227]. Human PrP transgenic models are also useful for the study of human susceptibility to animal prion strains. To date, the only recognized zoonotic prion disease is vCJD which first appeared in the United Kingdom in 1996 [228] and was soon proved to be caused by BSE-contaminated meat consumption [229]. The M129V polymorphism of human PrP is of special importance for human prion susceptibility. All vCJD definitely diagnosed cases are homozygous for the methionine allele, except for one recently found heterozygous case [230]. Transgenic mouse lines overexpressing human PrP harboring the M129 allele (Table 6) are successfully infected with BSE prions with a high resistance as reflected in the long survival times and partial attack rates that animals present [211,212,227,231]. These models mimic perfectly the real situation since virtually all of the UK population was exposed to BSE-contaminated meat, although just 232 cases of vCJD have been reported [232]. Transgenic mice overexpressing human PrP harboring the heterozygous M129V and homozygous V129 alleles (Table 2) have not been infected with BSE but vCJD transmission is successful, thus pointing to the risk that human to human secondary vCJD infection would pose for the population [233]. Sheep-passaged BSE can easier infect M129 human PrP transgenic mouse lines more when compared to cattle BSE [212,234]. For other prions not proved to be zoonotic, animal bioassays using transgenic models showed certain zoonotic potential for several agents like cattle atypical BSE prions and small ruminant classical scrapie [209,235,236]. More studies are needed for other emerging strains like small ruminant atypical scrapie and cervid chronic wasting disease prions [237,238]. In fact, chronic wasting disease prions have proved to have certain zoonotic potential [239].

Both for the study of the onset, progression, and molecular mechanisms involved in these diseases as well as for the test of possible treatments, transgenic mouse models of genetic TSEs would be of great usefulness. Something important to note is that practically all attempts to produce transgenic mouse models for human genetic TSEs using the human PrP sequence had been unsuccessful, ex-

cept for one recent model for GSS [224]. The rest of the successful transgenic mouse models for genetic TSEs have been made in the mouse, bank vole, or cattle PrP sequences or chimeric mouse/human PrP molecules.

7. Concluding Remarks

Despite the huge efforts done by the scientific community, NDs do not have any effective treatment these days. Numerous models have been generated based on the assumption that modeling the genetic "simpler" versions of NDs will provide useful insights to be later applied to the more common sporadic NDs. Unfortunately, in many cases, the generated models do not even fully reproduce the human phenotypes. Usually, the pathological and behavioral phenotypes displayed by the mice are milder, especially regarding behavioral alterations and neuron loss even though they were created using the same causative mutations (reviewed by [240]). This suggests the possible existence of unknown compensatory mechanisms in mice that may explain late-onset disorders and provide targets for novel strategies designed to extend neuronal function and survival [241]. In addition, it is also possible that this genetic "simpler" version of NDs is not only caused by mutations. In this sense, environmental factors might be the key to producing more reliable models. For instance, a high fat diet suministered to a transgenic mouse model of AD generated early prediabetic hyperinsulinemia that exacerbate AD pathology [242]. Other interesting option to generate models might be to produce transgenic mice with enhanced neuroprotective abilities. An example of such an approach is the overexpression of TREM2 (gene encoding receptor expressed on myeloid cells 2) in Tau transgenic mice, who showed that higher levels of TREM2 prevented neuronal loss and attenuated Tau pathology [243].

The partially manifested phenotypes are usually "cured" by candidate drugs in preclinical trials, but this success does not translate to the following human clinical trials. For instance, the *Tg2576* mice model for AD has been cured or their health has been improved by treatments evaluated in preclinical trials more than 300 times [244]. Therefore, projects aimed to "cure mice" by simply reducing the misfolded protein that is accumulating seem not to be working fine [245]. Indeed, it seems that misfolded protein accumulation in big aggregates is a protective mechanism given that shorter oligomers seem to be the most toxic species (reviewed in [148]).

Researchers from different NDs agree that although having a distinct molecular basis (in terms of the protein that gets misfolded and accumulated), behavioral phenotypes tend to overlap and the same happens at the molecular level regarding the pathways that led to cell death. Thus, a holistic and comprehensive approach aimed to unravel the neural death/survival circuits and their implication in different NDs may result in more successful candidates for the treatment of NDs. General pathways such as protein homeostasis, mitochondrial impairment, inflammation, oxidative stress, and cell death routes like apoptosis and autophagy are common to several NDs [246,247]. Along the same line, the mentioned above mice modeling also environmental factors, with enhanced neuron survival as well as mice aimed to model all these general pathways will provide therapeutic targets not necessarily restricted to one ND. These newer models will probably be generated using the CRISPR-Cas9 system [4]. CRISPR systems are adaptable immune mechanisms used by bacteria to protect themselves from foreign nucleic acids. Their combination with the Cas9 nuclease and a guide RNA allows directing Cas9 to a specific target DNA site using standard RNA-DNA complementarity base pairing rules (reviewed in [4]). This results in facile, rapid, and efficient modification of endogenous genes in a wide variety of cell types and novel organisms that have traditionally been difficult to manipulate genetically. In addition, the CRISPR-Cas9 system avoids random integration in the host DNA typically obtained in classic transgenesis but it may cause off-target edition.

Despite the lack of success in generating treatment options, transgenic mouse models have undoubtedly extended our understanding of NDs in the past years. Those models that at least show the progressive nature of the disease may serve to decipher the molecular mechanisms that end up producing neurodegeneration, thus generating potential options for early diagnosis and treatment before the neurons are irrevocably lost. In this way, combining the information provided by the "genetic" models with that provided by future "pathway-focused" ones may provide opportunities to create new strategies for drug development. Even little progress may have a direct impact on the aged population healthcare given that the prevalence of neurodegenerative diseases is rapidly growing.

Author Contributions

All authors (AMM, SC, NFB, JCE, and JMT) have contributed to the conception and design of the manuscript. AMM has been involved in drafting the manuscript and all authors (AMM, SC, NFB, JCE, and JMT) have been involved in revising it critically for important intellectual content. All authors (AMM, SC, NFB, JCE, and JMT) give final approval of the version to be published. All authors (AMM, SC, NFB, JCE, and JMT) have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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