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Genetically modified non-human primate models for research on neurodegenerative diseases

Ming-Tian Pan[1], Han Zhang[1], Xiao-Jiang Li[1], Xiang-Yu Guo[1,*]

[1] *Guangdong Key Laboratory of Non-human Primate Research*, *Guangdong-Hongkong-Macau Institute of CNS Regeneration*, *Jinan University*, *Guangzhou*, *Guangdong* 510632, *China*

ABSTRACT

Neurodegenerative diseases (NDs) are a group of debilitating neurological disorders that primarily affect elderly populations and include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Currently, there are no therapies available that can delay, stop, or reverse the pathological progression of NDs in clinical settings. As the population ages, NDs are imposing a huge burden on public health systems and affected families. Animal models are important tools for preclinical investigations to understand disease pathogenesis and test potential treatments. While numerous rodent models of NDs have been developed to enhance our understanding of disease mechanisms, the limited success of translating findings from animal models to clinical practice suggests that there is still a need to bridge this translation gap. Old World non-human primates (NHPs), such as rhesus, cynomolgus, and vervet monkeys, are phylogenetically, physiologically, biochemically, and behaviorally most relevant to humans. This is particularly evident in the similarity of the structure and function of their central nervous systems, rendering such species uniquely valuable for neuroscience research. Recently, the development of several genetically modified NHP models of NDs has successfully recapitulated key pathologies and revealed novel mechanisms. This review focuses on the efficacy of NHPs in modeling NDs and the novel pathological insights gained, as well as the challenges associated with the generation of such models and the complexities involved in their subsequent analysis.

Keywords: Neurodegeneration; Non-human primate; Macaque monkey; Animal model; Gene modification

INTRODUCTION

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are devastating neurological disorders characterized by the gradual loss of specific neuronal populations in affected brain regions. The primary risk factor for NDs is aging. With advancements in medical technologies and the increasing global population, NDs are expected to impose an intense burden on the medical system and affected families, both economically and emotionally, in the coming decades (Labzin et al., 2018; Rai et al., 2022; Ransohoff, 2016; Wyss-Coray, 2016).

Currently, no effective treatments exist that can reverse, halt, or significantly slow the progression of NDs, despite considerable efforts and advances in recent years. A key factor contributing to this challenge is the incomplete understanding of the mechanisms underlying ND pathogenesis. Patient samples are typically obtained at the end stage of the disease, hindering the acquisition of fresh tissues that display cardinal pathological events. Animal models serve as valuable tools for preclinical studies, especially for inheritable disease models that exhibit stable and reproducible phenotypes. Rodents are a primary resource for the development of ND models due to their small body size, short lifespan, potent reproductivity, low maintenance costs, and genetically modifiable embryonic stem cells, despite their distant phylogenetic proximity to humans. The discovery of causative gene mutations has led to the creation of various inheritable rodent ND models carrying these genes, exponentially expanding our understanding of NDs (Kabir et al., 2020; Wareham et al., 2022). However, although typical pathological features can be recapitulated in rodent ND models, rodent neurons exhibit a resistance to neurodegeneration (Tu et al., 2015). Evaluating the therapeutic impact on neurodegeneration using rodent models presents a significant challenge, as these models often lack the selective and overt neurodegeneration observed in patient

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*Corresponding author, E-mail: guosapphire@jnu.edu.cn

brains. This limitation is evident in the limited success of translating research from rodent models of NDs into clinical applications (Drummond & Wisniewski, 2017). Non-human primates (NHPs) are essential for neuroscience research given their striking similarity to humans in brain structure and function, as well as in their aging processes (Ding, 2013; Freire-Cobo et al., 2021; Yao, on behalf of the Construction Team of the KIZ Primate Facility, 2022). Recent advancements have led to the development of several genetically modified NHP models for NDs, revealing primate-specific mechanisms of ND pathogenesis. In this review, we explore important findings obtained from NHP models of NDs, with a focus on AD, PD, HD, and ALS, highlight novel pathogenic insights gained from such models, and discuss existing limitations, challenges, and perspectives in this field of study.

IMPORTANCE OF NHPs IN ND RESEARCH

After millions of years of evolution, the modern human brain has become exceptionally sophisticated, playing an essential role in information reception, processing, decision-making, and behavior (Dorus et al., 2004). While NDs often manifest as the deterioration of specific brain regions or neuronal populations, their pathology emerges and influences a broader context of neural circuits and cellular interactions, involving multiple cell types and cerebral regions. Therefore, faithful recapitulation of ND pathogenesis necessitates models with brain structures and functions that closely resemble those of humans. Being evolutionarily close to humans, NHPs possess complex brains. Cynomolgus (*Macaca fascicularis*), rhesus (*Macaca mulatta*), vervet (*Chlorocebus sabaeus*), and marmoset monkeys (*Callithrix jacchus*) are the most commonly used NHP species in research. In particular, Old World macaques share a common ancestor with humans dating back approximately 30 million years (Kanthaswamy et al., 2013), in contrast to mice, which diverged from humans around 70 million years ago (Kumar & Hedges, 2011). Thus, Old World primates present several advantages for modeling NDs, as outlined in Table 1.

Firstly, the cerebrum of Old World primates is structurally more similar to that of humans than rodents. On the external surface, the cerebra of humans and Old World primates are characterized by sulci and gyri, whereas rodent brains lack the cardinal feature of gyrification (Amiez et al., 2019; Garin et al., 2022; Zheng et al., 2022). Moreover, various structural differences exist between rodents and humans in subcortical regions that are selectively present in NHPs. For example, in both humans and monkeys, the striatum is divided into the caudate and putamen, a distinction absent in the rodent striatum (Bjerke et al., 2022; Joutsa et al., 2022; Lanciego & Vázquez, 2012; Zhu & Qiu, 2022). This complexity in cerebral structure shared by humans and monkeys may be attributed to their relatively prolonged developmental periods. Humans and macaques each require 280 and 160 days, respectively, for prenatal central nervous system (CNS) establishment, in contrast to rodents, which complete CNS development within 21 days (Table 1). Additionally, postnatal brain maturation in primates, including macaques and humans, requires years to complete, whereas the rodent brain matures in less than half a year (Yin et al., 2022). The persistence of neurogenesis in the subventricular zone (SVZ) and subgranular zone (SGZ) of the hippocampus is well-documented in adult mice, but its existence in primates remains a subject of debate (Eriksson et al., 1998; Hao et al., 2022; Li et al., 2023; Sorrells et al., 2018). These structural and developmental parallels extend to most other Old World monkeys, although macaques are more commonly used in neuroscience research.

Secondly, the composition, morphology, and distribution of cerebral cells in NHPs more closely resemble those in humans than in smaller animals. Glial cells, including astrocytes, microglia, and oligodendrocytes, are crucial for interacting with neurons and maintaining brain homeostasis. These cells also play critical roles in aging and neurodegeneration processes (Hickman et al., 2018; Lee et al., 2022; Von Bernhardi et al., 2015). The size, arborization, and proportion of glial cells to neurons in mice

Table 1 CNS trait comparisons across species

Species	Humans	Old World monkeys	Mice	References
Life span (years)	70–90	30–40	~2	Ackert-Bicknell et al., 2015; Asadi Shahmirzadi et al., 2020; Mattison & Vaughan, 2017; Moqri et al., 2023
Gestation period (days)	280	165–200	18	Liu et al., 2020; Souter et al., 2019; Weed et al., 2008
Neostriatum	Yes	Yes	No	D'Amours et al., 2011; Liu et al., 2020, 2021; Weed et al., 2008
Cerebral cortex Gyrification	Yes	Yes	No	Chen et al., 2023; Glasser et al., 2016; Wang et al., 2020
Circadian	Diurnal	Diurnal	Nocturnal	Jensen et al., 2013; Qin et al., 2015; Yan et al., 2020
Cortex thickness (mm)	2.5	2	0.85	Fischl & Dale, 2000; Hammelrath et al., 2016; Koo et al., 2012
Inter cortex communication	High	Moderate	Low	Semedo et al., 2019; Tsurugizawa et al., 2020
Natural AD, PD pathology	Yes	Yes	No	Arnsten et al., 2019; Heuer et al., 2012; Paspalas et al., 2018; Qiang et al., 2017
Average cerebral volume (cm^3)	1 350	80	0.5	Akeret et al., 2021; Johnson et al., 2023; Reveley et al., 2017; Sousa et al., 2017
Neuron number (billion)	85	6	0.07	Chen et al., 2023; Erö et al., 2018; Von Bartheld et al., 2016
Astrocyte to neuron ratio	1:1.4	1:2	1:3	Han et al., 2022; Khrameeva et al., 2020; Oberheim et al., 2006; Von Bartheld et al., 2016
Adult neurogenesis	No	No	Yes	Snyder et al., 2011; Sorrells et al., 2018
Average synapse per neuron	7 000	6 700	6 000	Drachman, 2005; O'Kusky & Colonnier, 1982; Schüz & Palm, 1989
Astrocyte size (in diameter, μm)	75	30	15	Oberheim et al., 2006; Robertson, 2014; Taber & Hurley, 2008
Astrocyte diversity	High	Moderate	Low	Chen et al., 2023; Endo et al., 2022; Zhou et al., 2019
Tau isoform in adult	6	6	3	Buée et al., 2000; Gambardella et al., 2023; McMillan et al., 2008

CNS: Central nervous system; BBB: Blood-brain barrier; AD: Alzheimer's disease; PD: Parkinson's disease.

differ substantially from those in primates (Geirsdottir et al., 2020; Taber & Hurley, 2008). For instance, NHP astrocytes develop more abundant processes compared to those in mice, resembling the astrocytes found in humans (Falcone et al., 2019; Matyash & Kettenmann, 2010; Oberheim et al., 2006; Rash et al., 2019). Additionally, astrocytes contribute to the blood-brain barrier (BBB) and regulate the exchange of materials between capillaries and cerebral parenchyma (Knox et al., 2022; Xu et al., 2013). Breakdown of the BBB is implicated in various degenerative diseases. Positron emission computed tomography (PET) radiotracers (Liu et al., 2016; Pike, 2009) and adeno-associated virus (AAV)-mediated cross-BBB transgenic studies (Goertsen et al., 2022; Terstappen et al., 2021) have revealed that BBB permeability in NHPs is more stringent than that in rodents, an essential consideration for exogenous gene delivery into brain cells to generate genetically modified NHP models. Neuronal function and survival depend on neurotrophic, nutritional, and structural support, as well as toxic material clearance, from glial cells (Allen & Lyons, 2018; Barres, 2008). Furthermore, glial cells are critical players in ND initiation and progression (Scheiblich et al., 2020; Stephenson et al., 2018; Ulland & Colonna, 2018). The comparability between NHP and human glial cells is therefore a marked advantage in the use of NHPs to model NDs.

Thirdly, NHPs also closely resemble humans in many other aspects, such as gene diversity, metabolism, aging processes, and behavioral versatility. The genomes of monkeys possess greater allelic diversity, offering a more faithful genomic context to mimic molecular pathogenesis. For example, genome-wide association studies (GWAS) have identified the APOE ε4 allele as a significant genetic risk factor for AD (Mahley et al., 2006, 2009). Unlike mice, which lack this allele, some monkey species are known carriers (Mahley et al., 2006; Poduri et al., 1994). Given the multifactorial etiology of NDs, the closer the resemblance to human conditions, the higher potential for developing effective models. Behavioral abnormalities comprise an important proportion of the clinical symptoms of NDs, an area where NHPs prove especially valuable. Depressive behavior and cognitive impairment, common features in ND patients, are challenging to assess in small animal models but can be evaluated in monkeys using well-established behavioral tests (Frye et al., 2022; Herndon et al., 1997).

AD NHP MODELS

AD is the most prevalent ND, affecting 7%–8% of individuals over the age of 65 globally and ranking as the sixth leading cause of death (Alzheimer's disease facts and figures, 2021; Scheltens et al., 2021). Symptomatically, AD is characterized by memory loss, cognitive dysfunction, and mental and behavioral abnormalities (Perrin et al., 2009). The two primary pathological hallmarks of AD are the excessive accumulation of extracellular amyloid-β (Aβ) and the presence of intracellular neurofibrillary tangles (NFTs). Other frequently observed associated pathologies include demyelination, neuroinflammation, brain atrophy, cerebral amyloid angiopathy, and synapse loss (Dubois et al., 2014). Although most cases of AD are late-onset and sporadic, lacking specific genetic mutations, a minor proportion are familial forms with early-onset symptoms caused by genetic mutations in the amyloid precursor protein (APP) and presenilin 1 or 2 genes (Kunkle et al., 2019; Masters et al., 2015). Following these genetic discoveries, many genetically modified mouse models expressing familial mutations driven by various promoters have been created (Götz & Ittner, 2008). However, despite successfully recapitulating prominent Aβ deposition, these mouse models do not induce other pathological hallmarks, notably Tau aggregation (McGowan et al., 2006; Sakakibara et al., 2019; Sasaguri et al., 2022). Furthermore, the salient neuronal loss observed in AD patients is not present in these Aβ transgenic mouse models (Elder et al., 2010; Flood et al., 2009). PET imaging data and functional correlation analysis have indicated that Tau pathology is more tightly correlated with AD symptom deterioration than Aβ deposition (Leuzy et al., 2020). Consequently, several human Tau transgenic mouse models have been generated (Eskandari-Sedighi et al., 2017; Götz et al., 2010; Myers & McGonigle, 2019). Although these mice exhibit Tau pathology, its distribution differs from that in AD patients, and the affected neurons remain resistant to degeneration, even when crossed with Aβ mouse lines (Esquerda-Canals et al., 2017). Minipigs have also been used to recapitulate AD pathogenesis using advanced gene manipulation tools (Jakobsen et al., 2013; Kragh et al., 2009), but they failed to exhibit typical pathology after a 3-year longitudinal study (Søndergaard et al., 2012). These findings underscore the necessity for establishing better AD models (Beckman & Morrison, 2021; King, 2018).

Recent investigations on aged NHPs have found the presence of naturally developed amyloid plaques and NFTs (Arnsten et al., 2019; Heuer et al., 2012; Paspalas et al., 2018). Importantly, the accumulation sites and spreading routes of Tau are the same as those reported in AD patients, strongly suggesting that monkeys are exceptional animals for modeling late-onset sporadic AD (Arnsten et al., 2021; Paspalas et al., 2018). Investigating the potential contributions of environmental toxic chemicals to AD pathogenesis, Yang et al. (2014) endeavored to induce AD in monkeys by formaldehyde or methanol exposure (Yang et al., 2014; Zhai et al., 2018). Attempts to create AD monkey models also include intracerebral or lateral ventricle injections of patient-derived or synthetic Aβ oligomers (AβOs), resulting in early pathological events, such as increased inflammation, reduced spines, and synaptic dysfunction, as well as the development of overt amyloid plaques and NFTs in multiple brain regions (Beckman et al., 2019; Forny-Germano et al., 2014). The use of younger animals in these studies may have influenced the outcomes, given that aging is a critical contributor to AD pathogenesis. Achieving widespread Aβ deposition across various brain regions is challenging due to the stringent BBB permeability in NHPs, although a recent study successfully created a monkey model with extensive Aβ accumulation in most brain regions via serial focal injections of synthetic AβOs into the cerebral parenchyma (Yue et al., 2021). This model also exhibited aberrant Tau phosphorylation and neuroinflammation, as evidenced by immunostaining, although brain atrophy and cognitive decline were not assessed (Yue et al., 2021). While it is not feasible to sacrifice a vast number of NHPs for disease progression examination, blood and cerebrospinal fluid (CSF) biomarkers, such as aβ42, aβ40, pTau, neurofilament light, soluble TREM2, IL6, and TNF-alpha, can non-invasively reflect pathological changes. PET imaging can also detect widespread amyloid plaque accumulation, warranting further integrative analysis of this model. Given the strong correlation between memory function decline and Tau hyperphosphorylation and aggregation

(Iaccarino et al., 2018; Perrin et al., 2009; Veitch et al., 2019), stereotaxic injections of AAV-expressing mutant human Tau have been performed in the entorhinal cortex of monkeys, a region where AD pathology initiates in its early stages (Beckman et al., 2021). Remarkably, the injected exogenous Tau demonstrated propagation through neural circuits, mimicking the spatiotemporal Tau pathology seen in AD, leading to increased levels of total Tau, phosphorylated Tau, neurofilament light, TNF-alpha, and soluble TREM2 in blood and CSF, similar to early AD stages (Beckman et al., 2021), but without changes in aβ42 and aβ40 levels, indicating a potential tauopathy-focused model due to the use of mutant Tau forms not typical in AD. Furthermore, the absence of functional assessment in this monkey model limits the validation of molecular results. Since the introduction of a small amount of mutant Tau was localized to a single site and AD pathology typically progresses over many years, extended longitudinal studies of such AD monkey models are needed to better understand the relationship between pathological changes and clinical manifestations.

PD NHP MODELS

Currently, more than 6 million people are affected by PD, making it the second most common ND (Bloem et al., 2021). PD is clinically diagnosed based on motor deficits, such as bradykinesia, rigidity, resting tremor, and postural instability. In addition, PD patients often experience non-motor problems, such as hyposmia, constipation, cognitive impairments, psychiatric disorders, and sleep abnormalities (Armstrong & Okun, 2020). Pathologically, PD is characterized by the presence of Lewy bodies and Lewy neurites in dopaminergic neurons in the substantia nigra (SN) (Kordower et al., 2013). Although most PD cases are sporadic, lacking specific causative gene mutations, approximately 10% are attributed to mutations in genes encoding α-Synuclein, PINK1, Parkin, LRRK2, and DJ-1, among others (Deng et al., 2018; Ye et al., 2023). Based on these genetic findings, various genetically modified PD mouse models have been generated by expressing PD-related gene mutations. However, none of these models has successfully simulated dopaminergic neuron degeneration characteristic of PD (Lee et al., 2012). Recent studies on mitochondrial dysfunction theory have suggested that mice with nigral disruptions in mitochondrial transcription A or respiratory chain complex component NDUFS2 develop progressive motor deficits (Beckstead & Howell, 2021; González-Rodríguez et al., 2021), offering a valuable model for therapies or drugs targeting mitochondrial dysfunction, despite the lack of identification of such gene mutations in PD patients.

Although PD was long thought to occur exclusively in humans, recent research has shown that senile monkeys can develop mild symptoms akin to early PD (Hurley et al., 2011). Furthermore, recent studies have revealed significant synucleinopathy in certain aged NHPs and the natural development of PD symptoms in a monkey. (Li et al., 2021a, 2021c), highlighting the unparalleled potential of NHPs for PD research. Given that creating transgenic NHP PD models is both expensive and time-consuming, chemically induced NHP models have emerged as popular alternatives. For example, 6-hydroxydopamine (6-OHDA, a hydroxylated analogue of dopamine), rotenone, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can selectively target dopaminergic neurons in the SN (Porras et al., 2012; Redmond et al., 1986; Tieu, 2011), inducing typical motor deficits, but without Lewy pathology. MPTP-induced monkey models have been widely used for drug testing and potential therapy evaluation for over four decades (Tieu, 2011). However, the phenotypes of this toxin-induced model are unstable and do not exactly mirror the slow progression characteristic of the disease. Recently developed protocols have attempted to address this issue employing stereotaxic injections of N-Methyl-4-Phenylpyridinium (MPP^+) into multiple sites within the unilateral SN, guided by magnetic resonance imaging (MRI) (Lei et al., 2015). Notably, α-synucleinopathy has been reported in monkey models subjected to repeated MPTP administration (Huang et al., 2018), paving the way for the development of more accurate PD animal models.

As Lewy bodies primarily consist of α-Synuclein, the overexpression of mutant human α-Synuclein in the SN of monkeys has been utilized to generate an NHP model of PD (Eslamboli et al., 2007; Kirik et al., 2003; Koprich et al., 2016). In marmosets, elevated α-Synuclein levels resulted in prominent tyrosine-positive cell loss within 16 weeks, along with the manifestation of head bias (Kirik et al., 2003). Mutant α-Synuclein has also been shown to cause accelerated pathology and symptom progression (Eslamboli et al., 2007). In macaques, introducing human A53T *α-Synuclein* through stereotaxic injection into the SN, using a virus driven by a universal promoter, led to the loss of over 50% of dopaminergic neurons within 4 months, effectively replicating nigrostriatal pathway degeneration, albeit without motor dysfunction and α-Synuclein spread (Koprich et al., 2016). Longer study on disease progression using this model may reveal advanced-stage PD. To mimic widespread expression, we previously generated an *α-Synuclein* transgenic PD monkey model by delivering lentivirus-expressing mutant *α-Synuclein* genes into the perivitelline space of fertilized eggs, resulting in reduced finger dexterity and cognitive impairment in 3-year-old monkeys (Niu et al., 2015). As aging is a risk factor for PD, Yang et al. (2015) administered intracerebral injections of mutant *α-Synuclein* into the SN of different aged monkeys and found that aging potently promoted α-Synuclein aggregation and synucleinopathy (Yang et al., 2015). Although α-Synuclein accumulation in dopaminergic neurons is toxic, knockdown of *α-Synuclein* by AAV-mediated RNA interference in the SN of monkeys has been shown to be detrimental (Collier et al., 2016), raising caution for therapies aiming to reduce endogenous α-Synuclein levels.

While earlier studies suggested that dopaminergic neurons in genetic mouse models of PD are resistant to degeneration (Blesa & Przedborski, 2014; Lee et al., 2012), recent developments in a *PINK1*-targeted PD monkey model established via CRISPR/Cas9 have shown that *PINK1* disruption results in severe neuronal loss (Chen et al., 2021; Yang et al., 2019c). Notably, some patients with early onset PD carry autosomal recessive mutations in the *PINK1* gene. In line with the loss-of-function mechanism associated with *PINK1* mutations in PD, several groups have attempted to generate PD monkey models based on CRISPR/Cas9-mediated *PINK1* knockout in fertilized monkey eggs (Chen et al., 2021; Yang et al., 2019c). Notably, *PINK1* gene knockout through fragment deletion results in severe neuronal loss in the monkey cerebral cortex (Yang et al., 2019c, 2022). However, most *PINK1* mutations in PD patients are point mutations, which may partially affect PINK1 function and cause age-dependent neurodegeneration. Therefore,

CRISPR/Cas9-mediated *PINK1* deletion may completely erase PINK1 function, enabling investigation of its essential role in neuronal survival in the primate brain (Yang et al., 2019b). Chen et al. (2021) used D10A nickase, a single-strand DNA cutting enzyme, to target *PINK1* in monkeys but did not observe PD symptoms in the generated models (Chen et al., 2021). Conversely, focal disruption of the *PINK1* and *DJ-1* genes in the adult brain has elicited important PD pathologies in monkeys, including significant loss of nigral dopaminergic neurons and increased phosphorylated α-Synuclein aggregates, as well as almost all classical PD symptoms, such as bradykinesia, tremor, and postural instability (Li et al., 2021b). This suggests that genetic mutation patterns and aging are both essential for developing PD symptoms in monkeys. However, the regional damage caused by heterogeneous gene manipulation could lead to mixed results, complicating the interpretation of these models. Yang et al. (2019b) indicated that PINK1 is more abundantly expressed under normal conditions in primates, whereas mouse PINK1 protein is undetectable, suggesting a potentially more significant role for PINK1 in primates than in mice.

ALS NHP MODELS

ALS is a rare, yet fatal ND characterized by progressive loss of motor neurons in the brain and spinal cord, leading to muscle atrophy and movement disorders (Grad et al., 2017). The disease occurs at an incidence of approximately 6 per 100 000 people, predominantly affecting elderly white populations (Talbott et al., 2016). Similar to AD and PD, over 90% of ALS patients are diagnosed without any identifiable gene mutation, while 5%–10% of cases are linked to genetic dysfunctions. Mutations in certain genes, such as TAR DNA-binding protein 43 (*TDP-43*), superoxide dismutase 1 (*SOD1*), fused in sarcoma (*FUS*), and *C9ORF72*, are implicated in ALS (Forman et al., 2007; Saberi et al., 2015). TDP-43 is a nuclear protein involved in gene transcription regulation, RNA processing, and protein homeostasis (Da Cruz & Cleveland, 2011; Lagier-Tourenne & Cleveland, 2009). In addition to ALS, *TDP-43* mutations are also implicated in fronto-temporal lobar degeneration (FTLD) and other neurological disorders, with cytoplasmic accumulation as a common pathological hallmark (Chen-Plotkin et al., 2010; Neumann et al., 2006). Normally residing in the nucleus, TDP-43 relocates to the cytoplasm during pathogenesiseliciting loss-of-function in the nucleus and toxicity in the cytoplasm (Mitchell et al., 2015).

Efforts to understand ALS pathogenesis have led to the development of several transgenic mouse models (Huang et al., 2012; Shan et al., 2010; Wang et al., 2015). However, none have successfully recapitulated the typical pathology, especially the cytoplasmic mislocalization of TDP-43 (Mitchell et al., 2015; Wils et al., 2010), highlighting the need to establish better animal models for ALS using larger animals. Cytoplasmic distribution of TDP-43 has been achieved in a transgenic pig model expressing human mutant *TDP-43* (Wang et al., 2015). Similarly, cytoplasmic distribution of mutant TDP-43 has been achieved in a macaque model expressing mutant *TDP-43* in the cortex and SN via stereotaxic viral vector delivery (Yin et al., 2019), corroborating earlier findings of mutant human TDP-43 in the neuronal cytoplasm of monkey spinal cord (Uchida et al., 2012). These results suggest that TDP-43-mediated neuronal pathology likely depends on species-specific factors. For instance, the primate-specific caspase-4 enzyme has been identified as responsible for cleaving mutant TDP-43, leading to its accumulation in the cytoplasm (Yin et al., 2019). The differences between mouse and monkey models of ALS underscore the unique contribution of NHPs to ALS research.

HD NHP MODELS

HD is a rare, monogenic, autosomal-dominant ND with complete penetrance. Its prevalence varies globally, with a higher rate in Western countries than in Asian populations. Pathogenically, HD is caused by CAG repeat expansion (>36 CAGs) in exon 1 of the huntingtin (*HTT*) gene, which translates to form polyglutamine (polyQ) repeats in the HTT protein (Bates et al., 2015; Yang et al., 2020). The expansion of polyQ induces conformational change in HTT and its aggregation in the brain, leading to preferential loss of striatal medium spiny neurons and extensive neurodegeneration in multiple brain regions as the disease progresses (Bates et al., 2015). Symptomatically, HD is characterized by involuntary movements, known as chorea, which typically manifest in midlife. The number of polyQ repeats is a determinant of disease onset, progression, and severity. To date, no effective treatment for HD is available (Bates et al., 2015).

Numerous rodent models of HD, carrying varying lengths of CAG repeats, have been established, although none have successfully replicated the prominent progressive loss of striatal neurons (Farshim & Bates, 2018; Lee & Heiman, 2022). The transgenic monkey model of HD, the first genetic NHP disease model, was created by injecting lentivirus into the perivitelline space of fertilized embryos (Yang et al., 2008a). However, although the lentivirus transferred the exogenous gene into host cell genome, the transgene insertion site and copy number were uncontrollable (Yang et al., 2008b), leading to pronounced phenotypic variation among the transgenic HD monkeys. Among these models, monkeys carrying 84 CAG repeats displayed severe phenotypes at an early postnatal stage, in contrast to mice with the same CAG repeat length, which showed subtle symptoms (Farshim & Bates, 2018; Yang et al., 2008a). Importantly, lentivirus-mediated transgenes can be transmitted through the germline, maintaining stable expression in monkeys (Moran et al., 2015; Putkhao et al., 2013), while first-generation offspring (F1) display CAG repeat instability during DNA replication, a cardinal feature of HD (Khampang et al., 2021). Longitudinal investigations on this model have found progressive changes in the striatum and hippocampus, along with motor and cognitive impairments (Chan et al., 2014; Kocerha et al., 2013), highlighting the value of monkeys in HD research. More recently, a novel HD monkey model was generated using focal delivery of an AAV2 and AAV2-retro mixture into the striatum, with rapid spread of mutant Htt into multiple brain regions, leading to cognitive decline and motor dysfunction (Weiss et al., 2022).

Similar to NHPs, transgenic swine models of HD demonstrate advantages over mice in mimicking neurodegeneration and motor disorders under the same HD transgene (Baxa et al., 2013; Schuldenzucker et al., 2017; Yang et al., 2010). Yan et al. (2018) successfully created a transgenic pig model of HD through CRISPR/Cas9-mediated knock-in (KI) in pig fibroblasts combined with somatic cell nuclear transfer cloning. This model, which expresses 150 CAG repeats driven by the endogenous *HTT* promoter, exhibited selective neurodegeneration in the striatum and movement impairments, effectively mimicking classic HD

pathology and features (Yan et al., 2018). Although the HD KI pig model is valuable, the monkey model is more suitable for emotional and psychiatric studies. Therefore, a more comprehensive understanding of HD pathogenesis will emerge from combining insights from both HD pig and monkey models.

PERSPECTIVES

Although genetic models account for only a small proportion of familial NDs, they often share a similar pathogenesis mechanism with sporadic cases. Thus, genetically modified NHPs are valuable tools for investigating disease pathogenesis. With the advancement of gene-editing techniques, particularly CRISPR/Cas9, several novel NHP models of NDs have been generated, offering new insights into their pathogenesis (Yang et al., 2021). However, precise gene editing with the CRISPR/Cas9 system or targeted KI of transgenes remains challenging, resulting in genetic heterogeneity and phenotype variation among individual models (Table 2), hindering efforts to unravel the underlying molecular mechanisms.

Aging is a key contributor to NDs, and the expression of disease-associated proteins (Aβ, Tau, and α-Synuclein) in the brains of old monkeys faithfully recapitulates neuropathology (Beckman et al., 2021; Yang et al., 2015; Yue et al., 2021). Research using NHP models of NDs has indicated that species-specific factors are critical for the development of core pathological events. For example, *PINK1* depletion in mouse brains does not cause neuronal loss, while in monkey brains, it results in severe neuronal loss, possibly due to the undetectable levels of PINK1 in rodent brains and abundant expression of PINK1 in primate brains under normal physiological conditions (Yang et al., 2019c, 2022). The primate-specific enzyme caspase-4, which cleaves TDP-43 to produce truncated TDP-43 that can be transported from the nucleus to cytoplasm, may explain why mouse models of ALS do not induce cytoplasmic mislocalization of TDP-43 (Yin et al., 2019). In HD, symptom onset is inversely correlated with the number of CAG repeats in exon 1 of the huntingtin gene. HD patients with more than 50 CAG repeats experience severe symptoms by middle age. However, mice carrying more than 100 CAG repeats may exhibit no obvious phenotype. Conversely, transgenic HD macaques with 80 CAG repeats show severe symptoms and early postnatal death (Yang et al., 2008a). The reasons for the milder phenotypes in HD mouse models remain unclear. As research continues, through both in-depth studies of current NHP models and the establishment of new NHP models, significant progress and novel insights into the pathogenesis of NDs are anticipated.

Despite considerable advancements, the widespread use of NHP models for NDs remains limited. A major challenge is the difficulty in scaling up most models for broader application. Due to their relatively low reproductive rates, longer generation intervals, and lack of germline integrating and gene-modifiable embryonic stem cells, it is difficult to produce NHP models through endogenous gene KI or knock-out in one-cell embryos, as is practicable in rodents (Tu et al., 2015). Although macaque cloning (Meng et al., 1997), especially through somatic cell nuclear transfer (Liu et al., 2018, 2019), has been achieved, the efficiency of this process is very low and needs further improvement. As most genetically based NDs are linked to point mutations, emerging technologies in base editing and prime editing (Yang et al., 2019a; Yeh et al., 2020) may facilitate the generation of better animal models carrying precise human genetic mutations. Recent research suggests that small molecules can revert human embryonic stem cells to an early blastomere state (Mazid et al., 2022), raising the possibility of attempting germline integration strategies in NHPs

NDs typically manifest in old age. Therefore, in animal models generated by germline genetic manipulations, disease pathologies are likely to appear as the animal ages. In this regard, strategies that can expedite the aging process may facilitate earlier development of disease symptoms. Given the longer lifespan and higher breeding costs of NHPs, utilizing older monkeys for ND research is a more practical approach. As NDs often selectively affect specific brain regions or

Table 2 NHP models of NDs generated by gene manipulation

Model	Targeted gene	Method	Pathology	Phenotype	References
PD	α-Synuclein	Substantia injection	Lewy body, DA neuronal loss	Head bias	Kirik et al., 2003; Koprich et al., 2016
		Transgenic by embryo injection	α-Synuclein, accumulation	Age-dependent fine motor deficits, anxiety, cognitive impairments	Niu et al., 2015
	PINK1	Gene disruption by CRISPR/Cas9 at embryo stage	Massive neuronal loss	Neurodevelopment dysfunction	Yang et al., 2019c, 2022
	PINK+DJ1	Gene disruption by CRISPR/Cas9 by substantia injection	Lewy body, DA neuronal degeneration, inflammation	Typical hemi-parkinsonism	Li et al., 2021b
AD	Tau	Overexpression of mutant human Tau by entorhinal cortex injection	Elevated inflammatory molecules and pTau, NFL in CSF and blood, Tau hyperphosphorylation and spread along circuitry network	Not available	Beckman et al., 2021
	Aβ	Serial injection of human AβOs into hippocampus of aged animals	Massive Aβ plaque across brain, overt intracellular Tau hyperphosphorylation	Not investigated	Yue et al., 2021
ALS	TDP-43	Overexpression of mutant human TDP-43 by lateral cerebral injection	TDP-43 accumulation in cytoplasm, salient neurodegeneration	Contralateral paralysis	Yin et al., 2019
HD	Htt	Transgenic by embryo injection of mutant Htt	CAG repeat dependent neuron inclusion and neurodegeneration	Prominent progressive motor function impairment	Yang et al., 2008a
		Overexpression of mutant human Htt by lateral striatum injection	Overt intracellular aggregates, mild neurodegeneration	Mild motor deficits	Weiss et al., 2022

neuronal subclusters, genetic mutations can be introduced into disease-associated neuronal cells or brain regions by stereotaxic injection of viral vectors with high efficiency. Recent studies employing this strategy have proven successful, leading to the creation of several monkey models of ND that have provided insights unattainable with smaller animal models (Yang et al., 2015, 2019b; Yin et al., 2015). Additionally, longitudinal phenotypic and genetic analyses of older monkeys may uncover cases of naturally occurring NDs. A team supported by the Chinese Academy of Sciences is currently conducting such research (Yao, on behalf of the Construction Team of the KIZ Primate Facility, 2022). This team has also launched the Primate Genome Project, which aims to sequence all primate genomes (Guo et al., 2023) and deepen our understanding of specific monkey models from an evolutionary perspective.

The development of AD typically spans many years (Arvanitakis et al., 2019). While patients with AD may exhibit mild cognitive impairment (MCI) in the early stages, MCI is also found in some aged individuals without AD neuropathology (Arvanitakis et al., 2019; Petersen et al., 2018). There is no clear demarcation between normal cognitive aging and early AD, both functionally and pathologically (Kirova et al., 2015; Sanford, 2017), suggesting that normal cognitive aging may serve as a natural model for studying the molecular mechanisms of early pathogenesis. Considering that Old World primates experience aging-related cognitive decline similar to humans (Hara et al., 2012; Herndon et al., 1997), they could provide an excellent model for investigating aging-related diseases.

Studying the neuropathology and mechanisms underlying selective neurodegeneration in NHPs models could yield highly valuable information specific to primates. Moreover, identifying primate-specific factors that contribute to selective neurodegeneration holds considerable potential for the generation of humanized rodent models, which could be widely used to investigate NDs and develop new therapies.

NHPs have long been used in preclinical drug safety and toxicity testing (Phillips et al., 2014; Sasseville & Mansfield, 2010). The FDA Modernization Act 2.0, enacted in December 2022, has eliminated the mandatory requirement for animal testing in new drug development (Han, 2023; Wadman, 2023). This change reflects advancements in artificial intelligence and organ-on-chip technologies (Joseph et al., 2022; Ma et al., 2021). Despite these developments, NHP models of NDs remain essential for enhancing translational success. Recent studies involving genetically modified NHPs have shown that they can more faithfully recapitulate the pathological changes observed in human brains, highlighting their value in ND research.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

X.J.L. and X.Y.G.: Conceived the idea for this review. M.T.P., H.Z., and X.Y.G.: Drafted the manuscript. X.J.L.: Revised the manuscript. All authors read and approved the final version of the manuscript.

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