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

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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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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.

REFERENCES

[No authors]. 2021. Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, **17**(3): 327−406.

Ackert-Bicknell CL, Anderson LC, Sheehan S, et al. 2015. Aging research using mouse models. *Current Protocols in Mouse Biology*, **5**(2): 95−133.

Akeret K, Van Niftrik CHB, Sebök M, et al. 2021. Topographic volume-standardization atlas of the human brain. *Brain Structure and Function*, **226**(6): 1699−1711.

Allen NJ, Lyons DA. 2018. Glia as architects of central nervous system formation and function. *Science*, **362**(6411): 181−185.

Amiez C, Sallet J, Hopkins WD, et al. 2019. Sulcal organization in the medial frontal cortex provides insights into primate brain evolution. *Nature Communications*, **10**(1): 3437.

Armstrong MJ, Okun MS. 2020. Diagnosis and treatment of parkinson disease: a review. *JAMA*, **323**(6): 548−560.

Arnsten AFT, Datta D, Leslie S, et al. 2019. Alzheimer's-like pathology in aging rhesus macaques: unique opportunity to study the etiology and treatment of Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, **116**(52): 26230−26238.

Arnsten AFT, Datta D, Preuss TM. 2021. Studies of aging nonhuman primates illuminate the etiology of early-stage Alzheimer's-like neuropathology: an evolutionary perspective. *American Journal of Primatology*, **83**(11): e23254.

Arvanitakis Z, Shah RC, Bennett DA. 2019. Diagnosis and management of dementia: review. *JAMA*, **322**(16): 1589−1599.

Asadi Shahmirzadi A, Edgar D, Liao CY, et al. 2020. Alpha-ketoglutarate, an endogenous metabolite, extends lifespan and compresses morbidity in aging mice. *Cell Metabolism*, **32**(3): 447−456.e446.

Barres BA. 2008. The mystery and magic of glia: a perspective on their roles in health and disease. *Neuron*, **60**(3): 430−440.

Bates GP, Dorsey R, Gusella JF, et al. 2015. Huntington disease. *Nature Reviews Disease Primers*, **1**: 15005.

Baxa M, Hruska-Plochan M, Juhas S, et al. 2013. A transgenic minipig model of Huntington's Disease. *Journal of Huntington's Disease*, **2**(1): 47−68.

Beckman D, Chakrabarty P, Ott S, et al. 2021. A novel tau-based rhesus monkey model of Alzheimer's pathogenesis. *Alzheimer's & Dementia*, **17**(6): 933−945.

Beckman D, Morrison JH. 2021. Towards developing a rhesus monkey model of early Alzheimer's disease focusing on women's health. *American Journal of Primatology*, **83**(11): e23289.

Beckman D, Ott S, Donis-Cox K, et al. 2019. Oligomeric Aβ in the monkey brain impacts synaptic integrity and induces accelerated cortical aging. *Proceedings of the National Academy of Sciences of the United States of America*, **116**(52): 26239−26246.

Beckstead MJ, Howell RD. 2021. Progressive parkinsonism due to mitochondrial impairment: lessons from the MitoPark mouse model. *Experimental Neurology*, **341**: 113707.

Bjerke IE, Cullity ER, Kjelsberg K, et al. 2022. DOPAMAP, high-resolution images of dopamine 1 and 2 receptor expression in developing and adult mouse brains. *Scientific Data*, **9**(1): 175.

Blesa J, Przedborski S. 2014. Parkinson's disease: animal models and dopaminergic cell vulnerability. *Frontiers in Neuroanatomy*, **8**: 155.

Bloem BR, Okun MS, Klein C. 2021. Parkinson's disease. *The Lancet*, **397**(10291): 2284−2303.

Buée L, Bussière T, Buée-Scherrer V, et al. 2000. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Research Reviews*, **33**(1): 95−130.

Chan AW, Xu Y, Jiang J, et al. 2014. A two years longitudinal study of a transgenic Huntington disease monkey. *BMC Neuroscience*, **15**: 36.

Chen A, Sun YD, Lei Y, et al. 2023. Single-cell spatial transcriptome reveals cell-type organization in the macaque cortex. *Cell*, **186**(17): 3726−3743.e24.

Chen ZZ, Wang JY, Kang Y, et al. 2021. *PINK1* gene mutation by pair truncated sgRNA/Cas9-D10A in cynomolgus monkeys. *Zoological Research*, **42**(4): 469−477.

Chen-Plotkin AS, Lee VMY, Trojanowski JQ. 2010. TAR DNA-binding protein 43 in neurodegenerative disease. *Nature Reviews Neurology*, **6**(4): 211−220.

Collier TJ, Redmond DE Jr, Steece-Collier K, et al. 2016. Is Alpha-synuclein loss-of-function a contributor to parkinsonian pathology?. Evidence from Non-human primates. *Frontiers in Neuroscience*, **10**: 12.

Da Cruz S, Cleveland DW. 2011. Understanding the role of TDP-43 and FUS/TLS in ALS and beyond. *Current Opinion in Neurobiology*, **21**(6): 904−919.

D'Amours G, Bureau G, Boily MJ, et al. 2011. Differential gene expression profiling in the mouse brain during motor skill learning: focus on the striatum structure. *Behavioural Brain Research*, **221**(1): 108−117.

Deng H, Wang P, Jankovic J. 2018. The genetics of Parkinson disease. *Ageing Research Reviews*, **42**: 72−85.

Ding SL. 2013. Comparative anatomy of the prosubiculum, subiculum, presubiculum, postsubiculum, and parasubiculum in human, monkey, and rodent. *Journal of Comparative Neurology*, **521**(18): 4145−4162.

Dorus S, Vallender EJ, Evans PD, et al. 2004. Accelerated evolution of nervous system genes in the origin of Homo sapiens. *Cell*, **119**(7): 1027−1040.

Drachman DA. 2005. Do we have brain to spare?. *Neurology*, **64**(12): 2004−2005.

Drummond E, Wisniewski T. 2017. Alzheimer's disease: experimental models and reality. *Acta Neuropathologica*, **133**(2): 155−175.

Dubois B, Feldman HH, Jacova C, et al. 2014. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *The Lancet Neurology*, **13**(6): 614−629.

Elder GA, Gama Sosa MA, De Gasperi R, et al. 2010. Presenilin transgenic mice as models of Alzheimer's disease. *Brain Structure and Function*, **214**(2-3): 127−143.

Endo F, Kasai A, Soto JS, et al. 2022. Molecular basis of astrocyte diversity and morphology across the CNS in health and disease. *Science*, **378**(6619): eadc9020.

Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. 1998. Neurogenesis in the adult human hippocampus. *Nature Medicine*, **4**(11): 1313−1317.

Erö C, Gewaltig MO, Keller D, et al. 2018. A cell atlas for the mouse brain. *Frontiers in Neuroinformatics*, **12**: 84.

Eskandari-Sedighi G, Daude N, Gapeshina H, et al. 2017. The CNS in inbred transgenic models of 4-repeat Tauopathy develops consistent tau seeding capacity yet focal and diverse patterns of protein deposition. *Molecular Neurodegeneration*, **12**(1): 72.

Eslamboli A, Romero-Ramos M, Burger C, et al. 2007. Long-term consequences of human alpha-synuclein overexpression in the primate ventral midbrain. *Brain*, **130**(Pt 3): 799–815.

Esquerda-Canals G, Montoliu-Gaya L, Güell-Bosch J, et al. 2017. Mouse models of Alzheimer's disease. *Journal of Alzheimer's Disease*, **57**(4): 1171−1183.

Falcone C, Wolf-Ochoa M, Amina S, et al. 2019. Cortical interlaminar astrocytes across the therian mammal radiation. *Journal of Comparative Neurology*, **527**(10): 1654−1674.

Farshim PP, Bates GP. 2018. Mouse models of huntington's disease. *In*: Precious SV, Rosser AE, Dunnett SB. Huntington's Disease. New York: Humana Press, 97–120.

Fischl B, Dale AM. 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, **97**(20): 11050−11055.

Flood DG, Lin YG, Lang DM, et al. 2009. A transgenic rat model of Alzheimer's disease with extracellular Aβ deposition. *Neurobiology of Aging*, **30**(7): 1078−1090.

Forman MS, Trojanowski JQ, Lee VMY. 2007. TDP-43: a novel neurodegenerative proteinopathy. *Current Opinion in Neurobiology*, **17**(5): 548−555.

Forny-Germano L, Lyra E Silva NM, Batista AF, et al. 2014. Alzheimer's disease-like pathology induced by amyloid-β oligomers in nonhuman primates. *The Journal of Neuroscience*, **34**(41): 13629−13643.

Freire-Cobo C, Edler MK, Varghese M, et al. 2021. Comparative neuropathology in aging primates: a perspective. *American Journal of Primatology*, **83**(11): e23299.

Frye BM, Craft S, Register TC, et al. 2022. Early Alzheimer's disease-like reductions in gray matter and cognitive function with aging in nonhuman primates. *Alzheimer's & Dementia*, **8**(1): e12284.

Gambardella JC, Schoephoerster W, Bondarenko V, et al. 2023. Expression of tau and phosphorylated tau in the brain of normal and hemiparkinsonian rhesus macaques. *Journal of Comparative Neurology*, **531**(11): 1198−1216.

Garin CM, Hori Y, Everling S, et al. 2022. An evolutionary gap in primate default mode network organization. *Cell Reports*, **39**(2): 110669.

Geirsdottir L, David E, Keren-Shaul H, et al. 2020. Cross-species single-cell analysis reveals divergence of the primate microglia program. *Cell*, **181**(3): 746.

Glasser MF, Coalson TS, Robinson EC, et al. 2016. A multi-modal parcellation of human cerebral cortex. *Nature*, **536**(7615): 171−178.

Goertsen D, Flytzanis NC, Goeden N, et al. 2022. AAV capsid variants with brain-wide transgene expression and decreased liver targeting after intravenous delivery in mouse and marmoset. *Nature Neuroscience*, **25**(1): 106−115.

González-Rodríguez P, Zampese E, Stout KA, et al. 2021. Disruption of mitochondrial complex I induces progressive parkinsonism. *Nature*, **599**(7886): 650−656.

Götz J, Gladbach A, Pennanen L, et al. 2010. Animal models reveal role for tau phosphorylation in human disease. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, **1802**(10): 860−871.

Götz J, Ittner LM. 2008. Animal models of Alzheimer's disease and frontotemporal dementia. *Nature Reviews Neuroscience*, **9**(7): 532−544.

Grad LI, Rouleau GA, Ravits J, et al. 2017. Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS). *Cold Spring Harbor Perspectives in Medicine*, **7**(8): a024117.

Guo YT, Shao Y, Bi XP, et al. 2023. Harvesting the fruits of the first stage of the primate genome project. *Zoological Research*, **44**(4): 725−728.

Hammelrath L, Škokić S, Khmelinskii A, et al. 2016. Morphological maturation of the mouse brain: an in vivo MRI and histology investigation. *NeuroImage*, **125**: 144−152.

Han JJ. 2023. FDA Modernization Act 2.0 allows for alternatives to animal testing. *Artificial Organs*, **47**(3): 449−450.

Han L, Wei XY, Liu CY, et al. 2022. Cell transcriptomic atlas of the non-human primate *Macaca fascicularis*. *Nature*, **604**(7907): 723–731.

Hao ZZ, Wei JR, Xiao DC, et al. 2022. Single-cell transcriptomics of adult macaque hippocampus reveals neural precursor cell populations. *Nature Neuroscience*, **25**(6): 805−817.

Hara Y, Rapp PR, Morrison JH. 2012. Neuronal and morphological bases of cognitive decline in aged rhesus monkeys. *AGE*, **34**(5): 1051−1073.

Herndon JG, Moss MB, Rosene DL, et al. 1997. Patterns of cognitive decline in aged rhesus monkeys. *Behavioural Brain Research*, **87**(1): 25−34.

Heuer E, Rosen RF, Cintron A, et al. 2012. Nonhuman primate models of Alzheimer-like cerebral proteopathy. *Current Pharmaceutical Design*, **18**(8): 1159−1169.

Hickman S, Izzy S, Sen P, et al. 2018. Microglia in neurodegeneration. *Nature Neuroscience*, **21**(10): 1359−1369.

Huang BH, Wu SH, Wang ZB, et al. 2018. Phosphorylated α-synuclein accumulations and lewy body-like pathology distributed in Parkinson's

disease-related brain areas of aged rhesus monkeys treated with MPTP. *Neuroscience*, **379**: 302−315.

Huang C, Tong JB, Bi FF, et al. 2012. Mutant TDP-43 in motor neurons promotes the onset and progression of ALS in rats. *Journal of Clinical Investigation*, **122**(1): 107−118.

Hurley PJ, Elsworth JD, Whittaker MC, et al. 2011. Aged monkeys as a partial model for Parkinson's disease. *Pharmacology Biochemistry and Behavior*, **99**(3): 324−332.

Iaccarino L, Tammewar G, Ayakta N, et al. 2018. Local and distant relationships between amyloid, tau and neurodegeneration in Alzheimer's Disease. *NeuroImage:Clinical*, **17**: 452−464.

Jakobsen JE, Johansen MG, Schmidt M, et al. 2013. Generation of minipigs with targeted transgene insertion by recombinase-mediated cassette exchange (RMCE) and somatic cell nuclear transfer (SCNT). *Transgenic Research*, **22**(4): 709−723.

Jensen TL, Kiersgaard MK, Sørensen DB, et al. 2013. Fasting of mice: a review. *Laboratory Animals*, **47**(4): 225−240.

Johnson GA, Tian YQ, Ashbrook DG, et al. 2023. Merged magnetic resonance and light sheet microscopy of the whole mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*, **120**(17): e2218617120.

Joseph X, Akhil V, Arathi A, et al. 2022. Comprehensive development in organ-on-a-chip technology. *Journal of Pharmaceutical Sciences*, **111**(1): 18−31.

Joutsa J, Moussawi K, Siddiqi SH, et al. 2022. Brain lesions disrupting addiction map to a common human brain circuit. *Nature Medicine*, **28**(6): 1249−1255.

Kabir MT, Uddin MS, Abdeen A, et al. 2020. Evidence linking protein misfolding to quality control in progressive neurodegenerative diseases. *Current Topics in Medicinal Chemistry*, **20**(23): 2025−2043.

Kanthaswamy S, Ng J, Satkoski Trask J, et al. 2013. The genetic composition of populations of cynomolgus macaques (*Macaca fascicularis*) used in biomedical research. *Journal of Medical Primatology*, **42**(3): 120−131.

Khampang S, Parnpai R, Mahikul W, et al. 2021. CAG repeat instability in embryonic stem cells and derivative spermatogenic cells of transgenic Huntington's disease monkey. *Journal of Assisted Reproduction and Genetics*, **38**(5): 1215−1229.

Khrameeva E, Kurochkin I, Han DD, et al. 2020. Single-cell-resolution transcriptome map of human, chimpanzee, bonobo, and macaque brains. *Genome Research*, **30**(5): 776−789.

King A. 2018. The search for better animal models of Alzheimer's disease. *Nature*, **559**(7715): S13−S15.

Kirik D, Annett LE, Burger C, et al. 2003. Nigrostriatal α-synucleinopathy induced by viral vector-mediated overexpression of human α-synuclein: a new primate model of Parkinson's disease. *Proceedings of the National Academy of Sciences of the United States of America*, **100**(5): 2884−2889.

Kirova AM, Bays RB, Lagalwar S. 2015. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed Research International*, **2015**: 748212.

Knox EG, Aburto MR, Clarke G, et al. 2022. The blood-brain barrier in aging and neurodegeneration. *Molecular Psychiatry*, **27**(6): 2659−2673.

Kocerha J, Liu YH, Willoughby D, et al. 2013. Longitudinal transcriptomic dysregulation in the peripheral blood of transgenic Huntington's disease monkeys. *BMC Neuroscience*, **14**: 88.

Koo BB, Schettler SP, Murray DE, et al. 2012. Age-related effects on cortical thickness patterns of the Rhesus monkey brain. *Neurobiology of Aging*, **33**(1): 200.e23−200.e31.

Koprich JB, Johnston TH, Reyes G, et al. 2016. Towards a non-human primate model of alpha-synucleinopathy for development of therapeutics for Parkinson's disease: optimization of AAV1/2 delivery parameters to drive sustained expression of alpha synuclein and dopaminergic degeneration in Macaque. *PLoS One*, **11**(11): e0167235.

Kordower JH, Olanow CW, Dodiya HB, et al. 2013. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain*, **136**(Pt 8): 2419–2431.

Kragh PM, Nielsen AL, Li J, et al. 2009. Hemizygous minipigs produced by random gene insertion and handmade cloning express the Alzheimer's disease-causing dominant mutation APPsw. *Transgenic Research*, **18**(4): 545−558.

Kumar S, Hedges SB. 2011. TimeTree2: species divergence times on the iPhone. *Bioinformatics*, **27**(14): 2023−2024.

Kunkle BW, Grenier-Boley B, Sims R, et al. 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nature Genetics*, **51**(3): 414−430.

Labzin LI, Heneka MT, Latz E. 2018. Innate immunity and neurodegeneration. *Annual Review of Medicine*, **69**: 437−449.

Lagier-Tourenne C, Cleveland DW. 2009. Rethinking ALS: the FUS about TDP-43. *Cell*, **136**(6): 1001−1004.

Lanciego JL, Vázquez A. 2012. The basal ganglia and thalamus of the long-tailed macaque in stereotaxic coordinates. A template atlas based on coronal, sagittal and horizontal brain sections. *Brain Structure and Function*, **217**(2): 613−666.

Lee H, Heiman M. 2022. Back-to-BACs in Huntington's disease modeling. *Neuron*, **110**(7): 1087−1089.

Lee HG, Wheeler MA, Quintana FJ. 2022. Function and therapeutic value of astrocytes in neurological diseases. *Nature Reviews Drug Discovery*, **21**(5): 339−358.

Lee Y, Dawson VL, Dawson TM. 2012. Animal models of Parkinson's disease: vertebrate genetics. *Cold Spring Harbor Perspectives in Medicine*, **2**(10): a009324.

Lei XG, Li H, Huang BH, et al. 2015. 1-Methyl-4-phenylpyridinium stereotactic infusion completely and specifically ablated the nigrostriatal dopaminergic pathway in rhesus macaque. *PLoS One*, **10**(5): e0127953.

Leuzy A, Smith R, Ossenkoppele R, et al. 2020. Diagnostic performance of RO948 F 18 Tau positron emission tomography in the differentiation of Alzheimer Disease from other neurodegenerative disorders. *JAMA Neurology*, **77**(8): 955−965.

Li H, Su LY, Yang LX, et al. 2021a. A cynomolgus monkey with naturally occurring Parkinson's disease. *National Science Review*, **8**(3): nwaa292.

Li H, Wu SH, Ma X, et al. 2021b. Co-editing *PINK1* and *DJ-1* Genes *Via* adeno-associated virus-delivered CRISPR/Cas9 system in adult monkey brain elicits classical parkinsonian phenotype. *Neuroscience Bulletin*, **37**(9): 1271−1288.

Li H, Yao YG, Hu XT. 2021c. Biological implications and limitations of a cynomolgus monkey with naturally occurring Parkinson's disease. *Zoological Research*, **42**(2): 138−140.

Li Y, Xu NN, Hao ZZ, et al. 2023. Adult neurogenesis in the primate hippocampus. *Zoological Research*, **44**(2): 315−322.

Liu H, Jin HJ, Yue XY, et al. 2016. Comparison of [^{11}C]TZ1964B and [^{18}F]MNI659 for PET imaging brain PDE10A in nonhuman primates. *Pharmacology Research & Perspectives*, **4**(5): e00253.

Liu XJ, Eickhoff SB, Caspers S, et al. 2021. Functional parcellation of human and macaque striatum reveals human-specific connectivity in the dorsal caudate. *NeuroImage*, **235**: 118006.

Liu Z, Cai YJ, Liao ZD, et al. 2019. Cloning of a gene-edited macaque monkey by somatic cell nuclear transfer. *National Science Review*, **6**(1): 101−108.

Liu Z, Cai YJ, Wang Y, et al. 2018. Cloning of macaque monkeys by somatic cell nuclear transfer. *Cell*, **172**(4): 881−887.e7.

Liu Z, Wang XJ, Newman N, et al. 2020. Anatomical and diffusion MRI brain atlases of the fetal rhesus macaque brain at 85, 110 and 135 days

gestation. *NeuroImage*, **206**: 116310.
Ma C, Peng YS, Li HT, et al. 2021. Organ-on-a-Chip: a new paradigm for drug development. *Trends in Pharmacological Sciences*, **42**(2): 119−133.
Mahley RW, Weisgraber KH, Huang YD. 2006. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, **103**(15): 5644−5651.
Mahley RW, Weisgraber KH, Huang YD. 2009. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *J Lipid Res*, **50 Suppl**(Suppl): S183–S188.
Masters CL, Bateman R, Blennow K, et al. 2015. Alzheimer's disease. *Nature Reviews Disease Primers*, **1**(1): 15056.
Mattison JA, Vaughan KL. 2017. An overview of nonhuman primates in aging research. *Experimental Gerontology*, **94**: 41−45.
Matyash V, Kettenmann H. 2010. Heterogeneity in astrocyte morphology and physiology. *Brain Research Reviews*, **63**(1-2): 2−10.
Mazid MA, Ward C, Luo ZW, et al. 2022. Rolling back human pluripotent stem cells to an eight-cell embryo-like stage. *Nature*, **605**(7909): 315−324.
McGowan E, Eriksen J, Hutton M. 2006. A decade of modeling Alzheimer's disease in transgenic mice. *Trends in Genetics*, **22**(5): 281−289.
McMillan P, Korvatska E, Poorkaj P, et al. 2008. Tau isoform regulation is region- and cell-specific in mouse brain. *Journal of Comparative Neurology*, **511**(6): 788−803.
Meng L, Ely JJ, Stouffer RL, et al. 1997. Rhesus monkeys produced by nuclear transfer. *Biology of Reproduction*, **57**(2): 454−459.
Mitchell JC, Constable R, So E, et al. 2015. Wild type human TDP-43 potentiates ALS-linked mutant TDP-43 driven progressive motor and cortical neuron degeneration with pathological features of ALS. *Acta Neuropathologica Communications*, **3**: 36.
Moqri M, Herzog C, Poganik JR, et al. 2023. Biomarkers of aging for the identification and evaluation of longevity interventions. *Cell*, **186**(18): 3758−3775.
Moran S, Chi T, Prucha MS, et al. 2015. Germline transmission in transgenic Huntington's disease monkeys. *Theriogenology*, **84**(2): 277−285.
Myers A, McGonigle P. 2019. Overview of transgenic mouse models for Alzheimer's disease. *Current Protocols in Neuroscience*, **89**(1): e81.
Neumann M, Sampathu DM, Kwong LK, et al. 2006. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*, **314**(5796): 130−133.
Niu YY, Guo XY, Chen YC, et al. 2015. Early Parkinson's disease symptoms in α-synuclein transgenic monkeys. *Human Molecular Genetics*, **24**(8): 2308−2317.
Oberheim NA, Wang XH, Goldman S, et al. 2006. Astrocytic complexity distinguishes the human brain. *Trends in Neurosciences*, **29**(10): 547−553.
O'Kusky J, Colonnier M. 1982. A laminar analysis of the number of neurons, glia, and synapses in the visual cortex (area 17) of adult macaque monkeys. *Journal of Comparative Neurology*, **210**(3): 278−290.
Paspalas CD, Carlyle BC, Leslie S, et al. 2018. The aged rhesus macaque manifests Braak stage III/IV Alzheimer's-like pathology. *Alzheimer's & Dementia*, **14**(5): 680−691.
Perrin RJ, Fagan AM, Holtzman DM. 2009. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature*, **461**(7266): 916−922.
Petersen RC, Lopez O, Armstrong MJ, et al. 2018. Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. *Neurology*, **90**(3): 126−135.
Phillips KA, Bales KL, Capitanio JP, et al. 2014. Why primate models matter. *American Journal of Primatology*, **76**(9): 801−827.
Pike VW. 2009. PET radiotracers: crossing the blood-brain barrier and surviving metabolism. *Trends in Pharmacological Sciences*, **30**(8): 431−440.
Poduri A, Gearing M, Rebeck GW, et al. 1994. Apolipoprotein E4 and beta amyloid in senile plaques and cerebral blood vessels of aged rhesus monkeys. *The American Journal of Pathology*, **144**(6): 1183−1187.
Porras G, Li Q, Bezard E. 2012. Modeling Parkinson's disease in primates: the MPTP model. *Cold Spring Harbor Perspectives in Medicine*, **2**(3): a009308.
Putkhao K, Kocerha J, Cho IK, et al. 2013. Pathogenic cellular phenotypes are germline transmissible in a transgenic primate model of Huntington's disease. *Stem Cells and Development*, **22**(8): 1198−1205.
Qiang W, Yau WM, Lu JX, et al. 2017. Structural variation in amyloid-β fibrils from Alzheimer's disease clinical subtypes. *Nature*, **541**(7636): 217−221.
Qin DD, Chu XX, Feng XL, et al. 2015. The first observation of seasonal affective disorder symptoms in Rhesus macaque. *Behavioural Brain Research*, **292**: 463−469.
Rai M, Curley M, Coleman Z, et al. 2022. Contribution of proteases to the hallmarks of aging and to age-related neurodegeneration. *Aging Cell*, **21**(5): e13603.
Ransohoff RM. 2016. How neuroinflammation contributes to neurodegeneration. *Science*, **353**(6301): 777−783.
Rash BG, Duque A, Morozov YM, et al. 2019. Gliogenesis in the outer subventricular zone promotes enlargement and gyrification of the primate cerebrum. *Proceedings of the National Academy of Sciences of the United States of America*, **116**(14): 7089−7094.
Redmond DE, Roth RH, Elsworth JD, et al. 1986. Fetal neuronal grafts in monkeys given methylphenyltetrahydropyridine. *The Lancet*, **327**(8490): 1125−1127.
Reveley C, Gruslys A, Ye FQ, et al. 2017. Three-dimensional digital template atlas of the macaque brain. *Cerebral Cortex*, **27**(9): 4463−4477.
Robertson JM. 2014. Astrocytes and the evolution of the human brain. *Medical Hypotheses*, **82**(2): 236−239.
Saberi S, Stauffer JE, Schulte DJ, et al. 2015. Neuropathology of amyotrophic lateral sclerosis and its variants. *Neurologic Clinics*, **33**(4): 855−876.
Sakakibara Y, Sekiya M, Saito T, et al. 2019. Amyloid-β plaque formation and reactive gliosis are required for induction of cognitive deficits in *App* knock-in mouse models of Alzheimer's disease. *BMC Neuroscience*, **20**(1): 13.
Sanford AM. 2017. Mild cognitive impairment. *Clinics in Geriatric Medicine*, **33**(3): 325−337.
Sasaguri H, Hashimoto S, Watamura N, et al. 2022. Recent advances in the modeling of Alzheimer's disease. *Frontiers in Neuroscience*, **16**: 807473.
Sasseville VG, Mansfield KG. 2010. Overview of known non-human primate pathogens with potential to affect colonies used for toxicity testing. *Journal of Immunotoxicology*, **7**(2): 79−92.
Scheiblich H, Trombly M, Ramirez A, et al. 2020. Neuroimmune connections in aging and neurodegenerative diseases. *Trends in Immunology*, **41**(4): 300−312.
Scheltens P, De Strooper B, Kivipelto M, et al. 2021. Alzheimer's disease. *The Lancet*, **397**(10284): 1577−1590.
Schuldenzucker V, Schubert R, Muratori LM, et al. 2017. Behavioral testing of minipigs transgenic for the Huntington gene-A three-year observational study. *PLoS One*, **12**(10): e0185970.
Schüz A, Palm G. 1989. Density of neurons and synapses in the cerebral cortex of the mouse. *Journal of Comparative Neurology*, **286**(4): 442−455.
Semedo JD, Zandvakili A, Machens CK, et al. 2019. Cortical areas interact through a communication subspace. *Neuron*, **102**(1): 249−259.e4.
Shan X, Chiang PM, Price DL, et al. 2010. Altered distributions of Gemini of coiled bodies and mitochondria in motor neurons of *TDP-43* transgenic mice. *Proceedings of the National Academy of Sciences of the United*

States of America, **107**(37): 16325−16330.

Snyder JS, Soumier A, Brewer M, et al. 2011. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*, **476**(7361): 458−461.

Søndergaard LV, Ladewig J, Dagnæs-Hansen F, et al. 2012. Object recognition as a measure of memory in 1–2 years old transgenic minipigs carrying the APPsw mutation for Alzheimer's disease. *Transgenic Research*, **21**(6): 1341−1348.

Sorrells SF, Paredes MF, Cebrian-Silla A, et al. 2018. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature*, **555**(7696): 377−381.

Sousa AMM, Meyer KA, Santpere G, et al. 2017. Evolution of the human nervous system function, structure, and development. *Cell*, **170**(2): 226−247.

Souter V, Painter I, Sitcov K, et al. 2019. Maternal and newborn outcomes with elective induction of labor at term. *American Journal of Obstetrics and Gynecology*, **220**(3): 273.e1−273.e11.

Stephenson J, Nutma E, Van Der Valk P, et al. 2018. Inflammation in CNS neurodegenerative diseases. *Immunology*, **154**(2): 204−219.

Taber KH, Hurley RA. 2008. Astroglia: not just glue. *The Journal of Neuropsychiatry and Clinical Neurosciences*, **20**(2): iv−129.

Talbott EO, Malek AM, Lacomis D. 2016. The epidemiology of amyotrophic lateral sclerosis. *Handbook of Clinical Neurology*, **138**: 225−238.

Terstappen GC, Meyer AH, Bell RD, et al. 2021. Strategies for delivering therapeutics across the blood-brain barrier. *Nature Reviews Drug Discovery*, **20**(5): 362−383.

Tieu K. 2011. A guide to neurotoxic animal models of Parkinson's disease. *Cold Spring Harbor Perspectives in Medicine*, **1**(1): a009316.

Tsurugizawa T, Tamada K, Ono N, et al. 2020. Awake functional MRI detects neural circuit dysfunction in a mouse model of autism. *Science Advances*, **6**(6): eaav4520.

Tu ZC, Yang WL, Yan S, et al. 2015. CRISPR/Cas9: a powerful genetic engineering tool for establishing large animal models of neurodegenerative diseases. *Molecular Neurodegeneration*, **10**: 35.

Uchida A, Sasaguri H, Kimura N, et al. 2012. Non-human primate model of amyotrophic lateral sclerosis with cytoplasmic mislocalization of TDP-43. *Brain*, **135**(Pt 3): 833–846.

Ulland TK, Colonna M. 2018. TREM2 - a key player in microglial biology and Alzheimer disease. *Nature Reviews Neurology*, **14**(11): 667−675.

Veitch DP, Weiner MW, Aisen PS, et al. 2019. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's disease neuroimaging initiative. *Alzheimer's & Dementia*, **15**(1): 106−152.

Von Bernhardi R, Eugenín-Von Bernhardi L, Eugenín J. 2015. Microglial cell dysregulation in brain aging and neurodegeneration. *Frontiers in Aging Neuroscience*, **7**: 124.

Von Bartheld CS, Bahney J, Herculano-Houzel S. 2016. The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting. *Journal of Comparative Neurology*, **524**(18): 3865−3895.

Wadman M. 2023. FDA no longer has to require animal testing for new drugs. *Science*, **379**(6628): 127−128.

Wang GH, Yang HQ, Yan S, et al. 2015. Cytoplasmic mislocalization of RNA splicing factors and aberrant neuronal gene splicing in TDP-43 transgenic pig brain. *Molecular Neurodegeneration*, **10**: 42.

Wang QX, Ding SL, Li Y, et al. 2020. The allen mouse brain common coordinate framework: a 3D reference atlas. *Cell*, **181**(4): 936−953.20.

Wareham LK, Liddelow SA, Temple S, et al. 2022. Solving neurodegeneration: common mechanisms and strategies for new treatments. *Molecular Neurodegeneration*, **17**(1): 23.

Weed MR, Wilcox KM, Ator NA, et al. 2008. Consistent, high-level ethanol consumption in pig-tailed macaques via a multiple-session, limited-intake, oral self-dosing procedure. *Alcoholism:Clinical and Experimental Research*, **32**(6): 942−951.

Weiss AR, Liguore WA, Brandon K, et al. 2022. A novel rhesus macaque model of Huntington's disease recapitulates key neuropathological changes along with motor and cognitive decline. *eLife*, **11**: e77568.

Wils H, Kleinberger G, Janssens J, et al. 2010. TDP-43 transgenic mice develop spastic paralysis and neuronal inclusions characteristic of ALS and frontotemporal lobar degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, **107**(8): 3858−3863.

Wyss-Coray T. 2016. Ageing, neurodegeneration and brain rejuvenation. *Nature*, **539**(7628): 180−186.

Xu R, Zanotti-Fregonara P, Zoghbi SS, et al. 2013. Synthesis and evaluation in monkey of [^{18}F]4-fluoro-*N*-methyl-*N*-(4-(6-(methylamino)pyrimidin-4-yl)thiazol-2-yl)benzami de ([^{18}F]FIMX): a promising radioligand for PET imaging of brain metabotropic glutamate receptor 1 (mGluR1). *Journal of Medicinal Chemistry*, **56**(22): 9146−9155.

Yan L, Smale L, Nunez AA. 2020. Circadian and photic modulation of daily rhythms in diurnal mammals. *European Journal of Neuroscience*, **51**(1): 551−566.

Yan S, Tu ZC, Liu ZM, et al. 2018. A huntingtin knockin pig model recapitulates features of selective neurodegeneration in Huntington's Disease. *Cell*, **173**(4): 989−1002.e13.

Yang DS, Wang CE, Zhao BT, et al. 2010. Expression of Huntington's disease protein results in apoptotic neurons in the brains of cloned transgenic pigs. *Human Molecular Genetics*, **19**(20): 3983−3994.

Yang HM, Yang S, Jing L, et al. 2020. Truncation of mutant huntingtin in knock-in mice demonstrates exon1 huntingtin is a key pathogenic form. *Nature Communications*, **11**(1): 2582.

Yang L, Yang B, Chen J. 2019a. One prime for all editing. *Cell*, **179**(7): 1448−1450.

Yang MF, Miao JY, Rizak J, et al. 2014. Alzheimer's disease and methanol toxicity (part 2): lessons from four rhesus macaques (*Macaca mulatta*) chronically fed methanol. *Journal of Alzheimer's Disease*, **41**(4): 1131−1147.

Yang SH, Cheng PH, Banta H, et al. 2008a. Towards a transgenic model of Huntington's disease in a non-human primate. *Nature*, **453**(7197): 921−924.

Yang SH, Cheng PH, Sullivan RT, et al. 2008b. Lentiviral integration preferences in transgenic mice. *Genesis*, **46**(12): 711−718.

Yang WL, Chen XS, Li SH, et al. 2021. Genetically modified large animal models for investigating neurodegenerative diseases. *Cell & Bioscience*, **11**(1): 218.

Yang WL, Guo XY, Tu ZC, et al. 2022. PINK1 kinase dysfunction triggers neurodegeneration in the primate brain without impacting mitochondrial homeostasis. *Protein & Cell*, **13**(1): 26−46.

Yang WL, Li SH, Li XJ. 2019b. A CRISPR monkey model unravels a unique function of PINK1 in primate brains. *Molecular Neurodegeneration*, **14**(1): 17.

Yang WL, Liu YB, Tu ZC, et al. 2019c. CRISPR/Cas9-mediated *PINK1* deletion leads to neurodegeneration in rhesus monkeys. *Cell Research*, **29**(4): 334−336.

Yang WL, Wang GH, Wang CE, et al. 2015. Mutant alpha-synuclein causes age-dependent neuropathology in monkey brain. *The Journal of Neuroscience*, **35**(21): 8345−8358.

Yao YG, on behalf of the Construction Team of the KIZ Primate Facility. 2022. Towards the peak: the 10-year journey of the national research facility for phenotypic and genetic analysis of model animals (Primate Facility) and a call for international collaboration in non-human primate research. *Zoological Research*, **43**(2): 237−240.

Ye H, Robak LA, Yu MG, et al. 2023. Genetics and Pathogenesis of Parkinson's Syndrome. *Annual Review of Pathology:Mechanisms of*

Disease, **18**: 95−121.

Yeh WH, Shubina-Oleinik O, Levy JM, et al. 2020. In vivo base editing restores sensory transduction and transiently improves auditory function in a mouse model of recessive deafness. *Science Translational Medicine*, **12**(546): eaay9101.

Yin P, Guo XY, Yang WL, et al. 2019. Caspase-4 mediates cytoplasmic accumulation of TDP-43 in the primate brains. *Acta Neuropathologica*, **137**(6): 919−937.

Yin P, Li SH, Li XJ, et al. 2022. New pathogenic insights from large animal models of neurodegenerative diseases. *Protein & Cell*, **13**(10): 707−720.

Yin P, Tu ZC, Yin A, et al. 2015. Aged monkey brains reveal the role of ubiquitin-conjugating enzyme UBE2N in the synaptosomal accumulation of mutant huntingtin. *Human Molecular Genetics*, **24**(5): 1350−1362.

Yue F, Feng S, Lu CL, et al. 2021. Synthetic amyloid-β oligomers drive early pathological progression of Alzheimer's disease in nonhuman primates. *iScience*, **24**(10): 103207.

Zhai RW, Rizak J, Zheng N, et al. 2018. Alzheimer's disease-like pathologies and cognitive impairments induced by formaldehyde in non-human primates. *Current Alzheimer Research*, **15**(14): 1304−1321.

Zheng N, Li M, Wu Y, et al. 2022. A novel technology for *in vivo* detection of cell type-specific neural connection with AQP1-encoding rAAV2-retro vector and metal-free MRI. *NeuroImage*, **258**: 119402.

Zhou B, Zuo YX, Jiang RT. 2019. Astrocyte morphology: diversity, plasticity, and role in neurological diseases. *CNS Neuroscience & Therapeutics*, **25**(6): 665−673.

Zhu JW, Qiu AQ. 2022. Chinese adult brain atlas with functional and white matter parcellation. *Scientific Data*, **9**(1): 352.