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Ageing and Neurodegenerative Diseases

Review

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Modeling neurodegenerative diseases using non-human primates: advances and challenges

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Abstract

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are pathologically characterized by progressive loss of selective populations of neurons in the affected brain regions and clinically manifested by cognitive, motor, and psychological dysfunctions. Since aging is the major risk factor for NDs and the elderly population is expected to expand considerably in the coming decades, the prevalence of NDs will significantly increase, leading to a greater medical burden to society and affected families. Despite extensive research on NDs, no effective therapy is available for NDs, largely due to a lack of complete understanding of the pathogenesis of NDs. Although research on small animal and rodent models has provided tremendous knowledge of molecular mechanisms of disease pathogenesis, few translational successes have been reported in clinical trials. In particular, most genetically modified rodent models are unable to recapitulate striking and overt neurodegeneration seen in the patient brains. Non-human primates (NHPs) are the most relevant laboratory animals to humans, and recent studies using NHP neurodegeneration models have uncovered important pathological features of NDs. Here, we review the unique features of NHPs for modeling NDs and new insights into AD, PD, and ALS gained from animal models, highlight the contribution of gene editing techniques to establishing NHP models, and discuss the challenges of investigating NHP models.

Keywords: Neurodegeneration, non-human primate, gene editing

INTRODUCTION

Neurodegenerative diseases (NDs) represent a group of devastating neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). NDs are characterized by progressive loss of specific populations of neurons in the affected brain regions. NDs always manifest clinical symptoms in old age. As the life span and global population increase, the number of ND patients is expected to rapidly rise in the coming decades[1-4].

At present, no therapy can reverse, halt, or slow NDs, although a lot of progress has been made in the past decades. One of the important reasons for the failure to effectively treat NDs is that the pathogenesis of NDs is still an enigma. Although most (> 90%) NDs are sporadic, small populations of familial NDs are found to carry genetic mutations. Identification of these genetic defects enabled the generation of gene-modified animals, which provide important animal models for us to investigate the pathogenesis of NDs[5,6]. Of these animal models, rodents are widely used and serve as essential animal models for investigating almost all types of NDs, largely because of their small size, fast breeding, and short generation time, as well as the available embryonic stem cells (ESC) that allow for genetically modifying endogenous rodent genes efficiently. As a result, several ND rodent models have been created, and investigation of these animal models has generated a wealth of information regarding the pathological changes and mechanisms of NDs. Although most rodent models can recapitulate the important pathological hallmarks of NDs, overt neuronal loss is often missed[7], making it difficult to use rodent models to rigorously evaluate therapeutic effects on neurodegeneration. In line with this scenario, most therapeutic trials based on findings from rodent NDs models have failed clinically[8]. NHPs are closer to humans than other species of animals, especially in their brain structure and function, as well as the aging process[9,10]. Recently, several NHP ND models have been generated and provided new insights into ND pathogenesis. Here, we review the strengths of NHPs for ND investigation, highlight new pathogenic insights offered by NHP models of NDs with a focus on AD, PD, and ALS, and discuss challenges and perspectives for future studies.

UNIQUE ADVANTAGES OF NHPS FOR ND INVESTIGATION

The brain is the most complex and delicate organ of mammals, responsible for information reception, procession, decision making, and organism behavior. During evolutionary progress, primates developed a sophisticated central never system (CNS), leading to the most intelligent human being[11]. Laboratory NHPs primarily consist of cynomolgus (*Macaca fascicularis*), rhesus (*Macaca mulatta*), and marmoset (*Callithrix jacchus*). The first two are old world monkeys belonging to the macaque genus, descended from the same ancestor 1.8 million years ago[12], and share the same ancestors with humans around 30 million years ago, while the mouse was divergent from humans 70 million years ago[13]. Macaque monkeys are more proximal to humans phylogenetically and more widely used in biomedical research due to their unparalleled high level of similarity with humans in the following important aspects.

First, there is a tremendous similarity in brain structure between macaque monkeys and humans. Human and monkey brains are full of gyrus and sulci at the outer surface, whereas rodent brains lack the important feature of gyrification[14-16]. While there are several differences in brain anatomy between rodents and humans, these differences do not exist in monkeys when compared with humans. For example, the striatum, which is particularly affected in Huntington's disease, is divided into caudate and putamen in both monkey and human brains but lacks these two distinct parts in rodent brains[17-20]. The similar brain anatomy and structure in humans and non-human primates are likely due to the similar timelines for brain

development. For example, the complete formation of CNS in humans and macaque monkeys before birth requires about 280 and 160 days, respectively, which is significantly different from the rapid formation of the mouse brain in 18 days [Table 1]. In addition, the postnatal primate (macaques and human) brain takes several years to reach maturation, while the rodent brain needs less than half a year[21]. Adult neurogenesis is kept in the subventricular zone and subgranular zone of the hippocampus in mice throughout life, while it is controversial in primates[22-24].

Second, the composition and morphology of cell types in the human brain are more similar to those in the monkey brain than in small animal brains[25-27]. Astrocytes and microglia collaborate to sustain brain environment homeostasis, and they also play important roles in aging and neurodegeneration[28-30]. The soma size and morphology of glial cells, as well as their ratio to neurons in mice, differ significantly from those in the primate[31,32]. For example, astrocytes in the non-human primate brains develop more abundant processes in the same manner as human astrocytes than those in the mouse brain[33-36]. Astrocytes are a core element of the blood-brain barrier (BBB), which works at the interface of capillary blood vessels and cerebral parenchyma, stringently regulating the materials exchange[37,38]. BBB breakdown is a hallmark event in several degenerative diseases. Positron emission computed tomography (PET) radiotracers[39,40] and recent adeno-associated virus (AAV)-mediated transgene[41,42] studies have revealed the special role of the NHP BBB in expressing and distributing transgenes. Glial cells are essential for the survival of neurons by both providing neurotrophic, nutritional, and structural support and removing toxic insults[43,44]. It has been well documented that glial dysfunction plays a critical role in NDs[45-47]. Similarities in glial cells between non-human primates and humans are obviously an advantage for NHP models of NDs.

Non-human primates also closely resemble many aspects of humans in genomic regulation, aging process, metabolism, and physiology. The monkey genome holds more variations among individual alleles, offering a more faithful genomic context to interrogate molecular pathogenesis. For example, genome-wide association studies have established that the first genetic risk factor for AD is the APOE ε4 allele, which is present in primates but absent in rodents[48,49].

Non-human primates are particularly useful for examining behavioral abnormalities that also occur in NDs. It is well known that depressive behavior and cognitive impairment are the common features of patients with NDs. These phenotypes, which are hardly assessed in small animal models, can be evaluated in monkeys using well-established behavioral assessments[50,51].

NHP models of AD

AD is the most common neurodegenerative disease, the sixth leading cause of death, and 7%-8% of people over age 65 have AD[52,53]. The typical clinical symptoms of AD consist of memory loss, cognitive dysfunction, and mental as well as behavioral abnormalities[54]. Extracellular senile amyloid plaques and intracellular neurofibrillary tangles (NFTs) are two pathological hallmarks of AD. In addition, cerebral amyloid angiopathy, demyelination, neuroinflammation, brain atrophy, and synaptic ion dyshomeostasis are frequently detected in association with AD pathology[55]. More than 90% of AD patients are sporadic with amnesic manifestation in the mid-60s or later, while fewer than 10% of AD cases are familial form with early-onset symptoms caused by genetic mutations in the amyloid precursor protein (APP), presenilin 1, and presenilin 2 genes[56,57]. Based on these genetic findings, numerous transgenic mouse models expressing familial mutations driven by various promoters have been created[58]. However, although prominent Aβ deposition can be seen, obvious Tau accumulation, the other pathological hallmark, is hardly seen in these mouse models[59-61]. Further, these Aβ transgenic mouse models do not develop overt and robust neurodegeneration as seen in patients with AD[62,63]. Because brain imaging data indicate that symptom

Table 1. Comparison of CNS features across species

Species	Human	Macaque	Mouse
Life span (years)	70-90	30-40	~2
New striatum	Yes	Yes	No
Gestation (days)	280	155	18
Behavior reservoir	large	Moderate	Small
BBB permeability	Strict	Moderate	low
Gyrification	Yes	Yes	No
Circadian	Diurnal	Diurnal	Nocturnal
Cortex thickness (mm)	4-5	2-3	1
Inter cortex communication	High	Moderate	low
Naturally developed AD, PD pathology	Yes	Yes	No

CNS: Central never system; BBB: blood-brain barrier; AD: Alzheimer's disease; PD: Parkinson's disease.

deterioration of AD correlates with Tau aggregation more tightly than Aβ deposition[64], several mouse models expressing human Tau were established[65-67]. Some *Tau* transgenic mice show no obvious neuron loss, even after being crossed with Aβ mouse lines[68]. Many attempts have also been made to recapitulate AD pathogenesis in the minipig[69,70], but no typical pathology was detected in a three-year longitudinal study[71]. Thus, these findings underscore the urgent need to establish a better AD model[72,73].

Recent investigations have found that primates can naturally develop amyloid plaques and NFTs in old age[74-76]. Importantly, the Tau pathology initiates and is spread in the same manner as that in AD patients, strongly suggesting that monkeys possess unparalleled physical context for the occurrence of late-onset sporadic AD[75,77]. Since toxic chemicals in the environment may contribute to AD pathogenesis, Yang *et al.* performed methanol administration to induce an AD monkey model[78,79]. Several investigations attempted to make AD models by intracerebral or lateral ventricle administration of synthetic or patients' Aβ oligomers (AβO), which results in early pathological events, including reduced spines, increased inflammation, and synaptic dysfunction, but with no amyloid plaques or NFTs[80,81]. Since young animals were used in these studies, aging may be an important contributor to the appearance of typical AD pathology. A recent study achieved a remarkable and widespread distribution of massive Aβ aggregate across the entire brain via single focal delivery of synthetic AβOs into cerebral parenchyma, which triggered neuroinflammation and slight Tau phosphorylation, although no brain atrophy or cognition decline was detected[82]. Since Tau hyperphosphorylation and aggregation are considered more cardinal factors for dementia severity[54,83,84], injection of AAV expressing mutant human Tau into the monkey entorhinal cortex, a region in which early AD pathology initiates, was tried to create an AD model. Interestingly, exogenous Tau is spread into various brain regions, highly reminiscent of the AD patient brain, causing disease markers related to AD to rise in blood and CSF[85]. However, no functional examination was presented in studies of this AD monkey model. Because aging is the major risk for AD, more longitudinal studies of the above AD monkey models may reveal the relationship between behavioral phenotypes and pathological changes.

NHP models of PD

As the second most common neurodegenerative disease, Parkinson's disease (PD) affects more than 6.1 million people worldwide[86]. PD is clinically recognizable for dyskinesia, such as resting tremor, rigidity, poor balance, and bradykinesia, and it also frequently presents with constipation, hyposmia, and cognitive, psychiatric, and sleep problems[87]. Pathologically, PD is caused by progressive loss of substantia nigra (SN) dopaminergic neurons, which results from the intracellular accumulation of α-Synuclein, namely Lewy

bodies or Lewy neurites[88]. Similar to AD, most PD cases are sporadic, but roughly 10% of cases are familial, caused by mutations in the genes encoding α-Synuclein, PINK1, Parkin, LRRK2, and DJ-1[89]. Accordingly, many genetically modified mouse models were developed to carry the PD gene mutations, but none of them can recapitulate the dopamine neuron degeneration in PD[90].

PD has long been considered as a human-specific disease; however, recent studies revealed that aged NHPs display prominent synucleinopathy[91], and a monkey naturally showing PD symptoms was identified[92], underlining the great potential of NHPs for PD research. Due to technical difficulties in generating transgenic NHP PD models, most NHP models for PD were generated using chemical toxins. 6-hydroxydopamine (6-OHDA) (a hydroxylated analog of dopamine) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can selectively target SN dopaminergic neurons[93,94], inducing typical behavioral manifestations despite the absence of Lewy pathology. Since the 1980s, the MTPT-induced monkey model has been prevalent for drug and therapy tests[94]. However, phenotypes of this toxin-induced model are unstable and do not exactly mirror slow disease progression. Recently developed protocols attempt to address this issue by stereotaxic injection of MPTP into multiple SN sites[95]. Interestingly, in a monkey model with repeated MPTP administrations, alpha synucleinopathy was detected[96], which opens up a new avenue for researchers to establish a better PD animal model.

Since α-Synuclein is the core component of Lewy bodies, many attempts have been made to generate NHP models by overexpressing human mutant α-Synuclein in the monkey SN[97]. Highly efficient expression of A53T α-Synuclein in SN can be achieved by stereotaxic brain injection, giving rise to pathological hallmark Lewy neurites that can be detected four months post-surgery and loss of over 50% dopaminergic neurons[97]. However, no motor dysfunction and α-Synuclein spreading are displayed[97]. A longitudinal study of disease progression with this model in the future may bring novel insights. An α-Synuclein transgenic PD monkey model carrying a clinical mutation was generated by expressing mutant transgenes in fertilized embryos with lentivirus, and these monkeys showed impaired finger coordination and cognitive dysfunction at three years of age[98]. Because PD is an age-dependent disease, Yang *et al.* performed intracerebral injection of mutant α-Synuclein into the SN in monkeys at different ages and found that aging greatly promotes the accumulation of α-Synuclein and alpha synucleinopathy[99].

As described above, all genetically modified mouse models of PD are unable to develop degeneration of dopamine neurons, a key pathological hallmark[90,100]. However, recent studies on establishing PINK1-targeted monkeys via CRISPR/Cas9 indicate that severe neuronal loss occurs in the monkey brains when PINK1 is lost[101,102]. PINK1 mutations cause autosomal recessive PD with early-onset manifestation. Because of the loss of function mechanism for PD with PINK1 mutations, several groups tried to create PD monkey models by CRISPR/Cas9-mediated PINK1 knockout in fertilized monkey embryos[101,102]. It seems that a large DNA fragment deletion in the PINK1 gene mediated by CRISPR/Cas9 can lead to a severe loss of neurons in the monkey brain[101,103]. However, most PINK1 mutations in humans are point mutations that may partially affect PINK1's function to cause age-dependent neurodegeneration. Thus, CRISPR/Cas9-mediated deletion of PINK1 may completely eliminate the function of PINK1, allowing identification of its critical role in neuronal survival in the primate brain[104]. Indeed, Chen *et al.* used a single strand cutting enzyme D10A nickases to target monkey PINK1 but did not find PD symptoms in the generated monkey model[102]. Conversely, focal disruption of the PINK1 and DJ-1 genes in the adult monkey brain was able to mimic some PD pathology[105], suggesting that both types of genetic mutations and aging could be important for developing PD phenotypes in monkeys.

NHP models of ALS

ALS is a rare and fatal neurodegenerative disease caused by progressive loss of motor neurons in the brain and spinal cord, leading to muscular atrophy and movement disorder[106]. The prevalence of ALS is around 6 cases per 100,000, with a preference for elderly Caucasians[107]. Similar to AD and PD, most ALS patients are sporadic, and about 5%-10% of cases are caused by gene mutations. Mutations in the genes encoding TAR DNA-binding protein 43 (TDP-43), superoxide dismutase 1 (SOD1), fused in sarcoma (FUS), and C9ORF72 can result in ALS[108,109]. TDP-43 is a nuclear protein that is involved in a variety of cellular functions, including gene transcription, RNA processing, and protein homeostasis[110,111]. In addition to ALS, TDP-43 mutation is also associated with frontotemporal lobar degeneration (FTLD), as well as other neurological disorders and pathological conditions. Of the pathological changes in these diseases, cytoplastic TDP-43 accumulation is the common hallmark[112,113]. Normally, TDP-43 is located in the nuclei but redistributed in the cytoplasm under pathological conditions. Mislocation of TDP-43 in the cytoplasm could lead to loss of function in the nuclei and toxic function in the cytoplasm[114].

Several transgenic mouse models have been established to investigate ALS pathogenesis[115-117], but most fail to recapitulate the cytoplasmic mislocation of TDP-43[114,118]. This phenomenon thus encourages the establishment of new ALS animal models using large animals. A TDP-43 transgenic pig model created by expressing mutant TDP-43 in fertilized eggs displayed the cytoplasmic distribution of TDP-43[115]. In addition, a macaque monkey model, which was generated by stereotaxic delivery of a viral vector expressing mutant TDP-43 into the cortex and substantia nigra, showed the cytoplasmic distribution of mutant TDP-43, which is in contrast to the nuclear distribution of the same transgenic mutant TDP-43 in the mouse brain[119]. This finding is consistent with the previous report that exogenous mutant TDP-43 is distributed in the neuronal cytoplasm in the monkey spinal cord[120]. Thus, TDP-43-mediated neuronal pathology is apparently dependent on species-specific factors. In support of this, primate-specific caspase-4 is found to be responsible for the cleavage of mutant TDP-43 and its cytoplasmic accumulation[119]. Comparing mouse and monkey models of ALS also highlights the importance of using non-human primates to investigate NDs.

NHP models of HD

HD is an autosomal dominant neurodegenerative disease with full penetration, as well as a rare inherited monogenic disease with varied prevalence across the world. The Asian population has the lowest incidence, while Western countries have a much higher prevalence. HD is pathogenically caused by CAG repeat expansion (> 36 CAGs) in exon 1 of the HD gene, which is translated to the polyglutamine (polyQ) repeat in the protein huntingtin (HTT)[121,122]. The polyQ expansion renders HTT to misfold and aggregate in the patient's brain, resulting in the preferential loss of the medium spiny neurons in the striatum and extensive neurodegeneration in various brain regions as the disease progresses[122]. Clinically, HD is characterized by involuntary movement, called chorea. This symptom usually appears in middle life, and disease onset, progression, and severity correlate with polyQ number. Currently, there is no effective therapy available for HD[122].

Dozens of HD rodent models carrying various lengths of CAG repeats have been generated. However, none of them can mimic overt progressive striatal neuron death[123,124]. The transgenic HD monkey model is the first gene-modified monkey disease model[125], created by lentivirus injection into fertilized embryos. Lentivirus mediates transgene insertion into the host genome at random sites with uncontrollable copy numbers[126] such that the transgenic HD monkey model generated by this protocol displayed overt phenotypic heterogeneity. Among the first transgenic HD monkeys, animals with 84 CAG repeats showed severe phenotype at the early postnatal stage, while mice carrying the same length of CAG repeats merely displayed subtle symptoms[123,125]. However, lentivirus-mediated transgene expression is germline

transmissible with a stable expression level[127,128]. Importantly, the offspring of the founder animal displayed CAG repeat instability, a critical feature of HD[129]. In subsequent longitudinal investigations, researchers further revealed that this model could resemble progressive striatal and hippocampal morphometric changes as well as motor and cognition impairment, similar to clinical observation[130,131].

Recently, several transgenic swine HD models were also generated[132-134]; these models also showed more obvious neurodegeneration and motor disorders than that of mice with the same length of CAG repeats. Through CRISPR/Cas9-mediated knock-in (KI) on pig fibroblast cells and somatic cell nuclear transfer technique, a HD KI pig model was successfully created[135]. This model expresses 150 CAG repeats under the endogenous HTT promoter, leading to selective neurodegeneration as well as movement disorders, effectively mimicking typical HD pathology and clinic features. Importantly, similar to the transgenic HD monkey, the HD KI pig is also inheritable[135], making it possible to generate a large number of HD pigs in the future based on the potent reproductive capability of swine. Although the HD KI pig seems to be an ideal model, the macaque monkey model is more suitable for investigating emotional and psychiatric activity. Thus, combining HD pig and monkey models will bring us deeper insight into HD pathogenesis as well as advances in HD therapy.

CHALLENGES AND SOLUTIONS

With the development of gene editing technology, especially CRISPR/Cas9, several NHP models of NDs have been established and offer new insights into pathogenesis. For example, aging has been confirmed to be critical for age-dependent neurodegeneration, as expressing the disease proteins (Amyloid-β, Tau, and α-Synuclein) in the brains of old monkeys can faithfully recapitulate neuropathology[82,85,99]. Investigations on NHP models of NDs also revealed that species-dependent factors are critically involved in important pathological events. Depletion of PINK1 can lead to severe neuronal loss in the monkey brain but not in the mouse brain, which is largely due to abundant expression of PINK1 in the primate brain and undetectable level of PINK1 in the rodent brain[101,103]. The lack of cytoplasmic distribution of mutant TDP-43 in most mouse models is perhaps due to the absence of caspase-4, a primate-specific enzyme that can cleave TDP-43 to cause truncated TDP-43 to move from the nucleus to the cytoplasm[119]. With more in-depth studies and the establishment of additional non-human primate models of NDs, greater advances are expected, which will bring new insights into disease pathogenesis.

Despite the great progress that has been made, NHP models of NDs have not been used at a large scale. One key hurdle is that most models are hard to scale up for widespread application. Due to relatively low reproductive capability, a longer time for sexual maturity, and the absence of germline integrating ESC, it is challenging to generate NHP models by following rodent protocols to knock-in or knock-out the endogenous genes in one-cell stage embryos[7]. Although cloning of the macaque monkey[136], especially by somatic cell nuclear transfer[137,138], has been demonstrated to be feasible, the efficiency is suboptimal and remains to be improved. Since many NDs are caused by point mutation, newly emerging base editing and prime editing tools[139,140] will facilitate the generation of better animal models that can precisely mimic human genetic mutations. Recent research indicates that appropriate small molecules are able to direct human ESC to the early stage blastomere state[141], suggesting the opportunity to implement a germline integration strategy in non-human primates [Figure 1].

Aging is the biggest risk factor for ND incidence. When investigating animal models generated from germline genetic manipulations, the animals are likely to show phenotypes and neuropathology when they become old. In this regard, any treatments that can promote the aging process should presumably facilitate the development of disease phenotypes. Considering the high cost for maintaining non-human primates

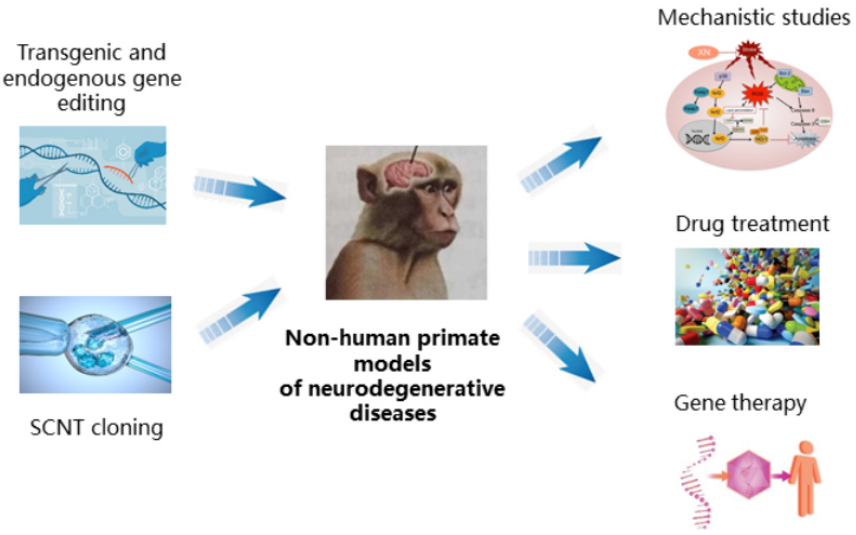

Figure 1. With the optimization of transgene and somatic cell nuclear transfer technique in non-human primate, more and better neurodegenerative disease monkey models will be generated in the future, which will in turn lead to promotion of molecular pathogenesis studies as well as treatment strategies such as drug development and gene therapy.

and their longer life span, it would be more appropriate to use monkeys at old ages to investigate NDs. Because NDs selectively affect distinct brain regions or specific types of neurons, it is feasible to selectively introduce genetic mutations in these brain regions or specific types of neurons by stereotaxic injection of viral vectors that can efficiently transduce neuronal cells. Recent studies using such a strategy have demonstrated its feasibility and generated several monkey models of NDs to offer novel findings that could not be obtained from small animal models[99,104,142]. Investigation of the neuropathology and mechanisms underlying selective neurodegeneration in non-human models should provide highly valuable information regarding pathogenesis for sporadic and familiar NDs, as both types of NDs share the same pathological and behavioral phenotypes. Uncovering the primate-specific factors that contribute to selective neurodegeneration is particularly important for the generation of humanized rodent models that can be widely used to investigate NDs and develop their therapies.

DECLARATIONS

Authors' contributions

Conceived the idea of this review article: Li XJ, Guo XY
Drafted the manuscript: Li B, He DJ, Guo XY
Revised the manuscript: Li XJ
Designed pictures: Guo XY
Completed the pictures: Li XJ

Available of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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REFERENCES

1. Rai M, Curley M, Coleman Z, Demontis F. Contribution of proteases to the hallmarks of aging and to age-related neurodegeneration. *Aging Cell* 2022;21:e13603. DOI PubMed PMC
2. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science* 2016;353:777-83. DOI PubMed
3. Labzin LI, Heneka MT, Latz E. Innate immunity and neurodegeneration. *Annu Rev Med* 2018;69:437-49. DOI PubMed
4. Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. *Nature* 2016;539:180-6. DOI PubMed PMC
5. Wareham LK, Liddelow SA, Temple S, et al. Solving neurodegeneration: common mechanisms and strategies for new treatments. *Mol Neurodegener* 2022;17:23. DOI PubMed PMC
6. Kabir MT, Uddin MS, Abdeen A, et al. Evidence linking protein misfolding to quality control in progressive neurodegenerative diseases. *Curr Top Med Chem* 2020;20:2025-43. DOI PubMed
7. Tu Z, Yang W, Yan S, Guo X, Li XJ. CRISPR/Cas9: a powerful genetic engineering tool for establishing large animal models of neurodegenerative diseases. *Mol Neurodegener* 2015;10:35. DOI PubMed PMC
8. Drummond E, Wisniewski T. Alzheimer's disease: experimental models and reality. *Acta Neuropathol* 2017;133:155-75. DOI PubMed PMC
9. Ding SL. Comparative anatomy of the prosubiculum, subiculum, presubiculum, postsubiculum, and parasubiculum in human, monkey, and rodent. *J Comp Neurol* 2013;521:4145-62. DOI PubMed
10. Freire-Cobo C, Edler MK, Varghese M, et al. Comparative neuropathology in aging primates: a perspective. *Am J Primatol* 2021;83:e23299. DOI PubMed PMC
11. Dorus S, Vallender EJ, Evans PD, et al. Accelerated evolution of nervous system genes in the origin of Homo sapiens. *Cell* 2004;119:1027-40. DOI PubMed
12. Kanthaswamy S, Ng J, Satkoski Trask J, et al. The genetic composition of populations of cynomolgus macaques (Macaca fascicularis) used in biomedical research. *J Med Primatol* 2013;42:120-31. DOI PubMed PMC
13. Kumar S, Hedges SB. TimeTree2: species divergence times on the iPhone. *Bioinformatics* 2011;27:2023-4. DOI PubMed PMC
14. Amiez C, Sallet J, Hopkins WD, et al. Sulcal organization in the medial frontal cortex provides insights into primate brain evolution. *Nat Commun* 2019;10:3437. DOI PubMed PMC
15. Zheng N, Li M, Wu Y, et al. A novel technology for in vivo detection of cell type-specific neural connection with AQP1-encoding rAAV2-retro vector and metal-free MRI. *Neuroimage* 2022;258:119402. DOI PubMed
16. Garin CM, Hori Y, Everling S, et al. An evolutionary gap in primate default mode network organization. *Cell Rep* 2022;39:110669. DOI PubMed PMC
17. Lanciego JL, Vázquez A. 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 Struct Funct* 2012;217:613-66. DOI PubMed PMC
18. Zhu J, Qiu A. Chinese adult brain atlas with functional and white matter parcellation. *Sci Data* 2022;9:352. DOI PubMed PMC
19. Joutsa J, Moussawi K, Siddiqi SH, et al. Brain lesions disrupting addiction map to a common human brain circuit. *Nat Med* 2022;28:1249-55. DOI PubMed PMC
20. Bjerke IE, Cullity ER, Kjelsberg K, Charan KM, Leergaard TB, Kim JH. DOPAMAP, high-resolution images of dopamine 1 and 2 receptor expression in developing and adult mouse brains. *Sci Data* 2022;9:175. DOI PubMed PMC
21. Yin P, Li S, Li XJ, Yang W. New pathogenic insights from large animal models of neurodegenerative diseases. *Protein Cell* 2022;13:707-20. DOI PubMed PMC
22. Hao ZZ, Wei JR, Xiao D, et al. Single-cell transcriptomics of adult macaque hippocampus reveals neural precursor cell populations. *Nat Neurosci* 2022;25:805-17. DOI PubMed

23. Sorrells SF, Paredes MF, Cebrian-Silla A, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature* 2018;555:377-81. DOI PubMed PMC
24. Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;4:1313-7. DOI PubMed
25. Fang R, Xia C, Close JL, et al. Conservation and divergence of cortical cell organization in human and mouse revealed by MERFISH. *Science* 2022;377:56-62. DOI PubMed PMC
26. Chen A, Liao S, Cheng M, et al. Spatiotemporal transcriptomic atlas of mouse organogenesis using DNA nanoball-patterned arrays. *Cell* 2022;185:1777-1792.e21. DOI PubMed
27. Han L, Wei X, Liu C, et al. Cell transcriptomic atlas of the non-human primate Macaca fascicularis. *Nature* 2022;604:723-31. DOI PubMed
28. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. *Nat Neurosci* 2018;21:1359-69. DOI PubMed PMC
29. Lee HG, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases. *Nat Rev Drug Discov* 2022;21:339-58. DOI PubMed PMC
30. Bernhardi R, Eugenin-von Bernhardi L, Eugenin J. Microglial cell dysregulation in brain aging and neurodegeneration. *Front Aging Neurosci* 2015;7:124. DOI PubMed PMC
31. Taber KH, Hurley RA. Astroglia: not just glue. *J Neuropsychiatry Clin Neurosci* 2008;20:iv-129. DOI PubMed
32. Geirsdottir L, David E, Keren-Shaul H, et al. Cross-species single-cell analysis reveals divergence of the primate microglia program. *Cell* 2020;181:746. DOI PubMed
33. Matyash V, Kettenmann H. Heterogeneity in astrocyte morphology and physiology. *Brain Res Rev* 2010;63:2-10. DOI PubMed
34. Rash BG, Duque A, Morozov YM, Arellano JI, Micali N, Rakic P. Gliogenesis in the outer subventricular zone promotes enlargement and gyrification of the primate cerebrum. *Proc Natl Acad Sci U S A* 2019;116:7089-94. DOI PubMed PMC
35. Falcone C, Wolf-Ochoa M, Amina S, et al. Cortical interlaminar astrocytes across the therian mammal radiation. *J Comp Neurol* 2019;527:1654-74. DOI PubMed PMC
36. Oberheim NA, Wang X, Goldman S, Nedergaard M. Astrocytic complexity distinguishes the human brain. *Trends Neurosci* 2006;29:547-53. DOI PubMed
37. Xu R, Zanotti-Fregonara P, Zoghbi SS, et al. Synthesis and evaluation in monkey of [(18)F]4-fluoro-N-methyl-N-(4-(6-(methylamino)pyrimidin-4-yl)thiazol-2-yl)benzamide ([(18)F]FIMX): a promising radioligand for PET imaging of brain metabotropic glutamate receptor 1 (mGluR1). *J Med Chem* 2013;56:9146-55.
38. Knox EG, Aburto MR, Clarke G, Cryan JF, O'Driscoll CM. The blood-brain barrier in aging and neurodegeneration. *Mol Psychiatry* 2022;27:2659-73. DOI PubMed PMC
39. Pike VW. PET radiotracers: crossing the blood-brain barrier and surviving metabolism. *Trends Pharmacol Sci* 2009;30:431-40. DOI PubMed PMC
40. Liu H, Jin H, Yue X, et al. Comparison of [^{11}C]TZ1964B and [^{18}F]MNI659 for PET imaging brain PDE10A in nonhuman primates. *Pharmacol Res Perspect* 2016;4:e00253.
41. Goertsen D, Flytzanis NC, Goeden N, et al. AAV capsid variants with brain-wide transgene expression and decreased liver targeting after intravenous delivery in mouse and marmoset. *Nat Neurosci* 2022;25:106-15. DOI PubMed
42. Terstappen GC, Meyer AH, Bell RD, Zhang W. Strategies for delivering therapeutics across the blood-brain barrier. *Nat Rev Drug Discov* 2021;20:362-83. DOI PubMed
43. Barres BA. The mystery and magic of glia: a perspective on their roles in health and disease. *Neuron* 2008;60:430-40. DOI PubMed
44. Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. *Science* 2018;362:181-5. DOI PubMed PMC
45. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. *Immunology* 2018;154:204-19. DOI PubMed PMC
46. Scheiblich H, Trombly M, Ramirez A, Heneka MT. Neuroimmune connections in aging and neurodegenerative diseases. *Trends Immunol* 2020;41:300-12. DOI PubMed
47. Ulland TK, Colonna M. TREM2 - a key player in microglial biology and Alzheimer disease. *Nat Rev Neurol* 2018;14:667-75. DOI PubMed
48. Poduri A, Gearing M, Rebeck GW, Mirra SS, Tigges J, Hyman BT. Apolipoprotein E4 and beta amyloid in senile plaques and cerebral blood vessels of aged rhesus monkeys. *Am J Pathol* 1994;144:1183-7. PubMed PMC
49. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A* 2006;103:5644-51. DOI PubMed PMC
50. Herndon JG, Moss MB, Rosene DL, Killiany RJ. Patterns of cognitive decline in aged rhesus monkeys. *Behavioural Brain Research* 1997;87:25-34. DOI PubMed
51. Frye BM, Craft S, Register TC, et al. Early Alzheimer's disease-like reductions in gray matter and cognitive function with aging in nonhuman primates. *Alzheimers Dement (N Y)* 2022;8:e12284. DOI PubMed PMC
52. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet* 2021;397:1577-90. DOI PubMed PMC
53. Alzheimer's disease facts and figures. *Alzheimers Dement* 2021;17:327-406. DOI PubMed
54. Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature*

2009;461:916-22. DOI PubMed PMC
55. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *The Lancet Neurology* 2014;13:614-29. DOI PubMed
56. Kunkle BW, Grenier-Boley B, Sims R, et al; Alzheimer Disease Genetics Consortium (ADGC); European Alzheimer's Disease Initiative (EADI); Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE); Genetic and Environmental Risk in AD/Defining Genetic; Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES). Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet* 2019;51:414-30. DOI PubMed PMC
57. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primers* 2015;1:15056. DOI PubMed
58. Götz J, Ittner LM. Animal models of Alzheimer's disease and frontotemporal dementia. *Nat Rev Neurosci* 2008;9:532-44. DOI PubMed
59. Sakakibara Y, Sekiya M, Saito T, Saido TC, Iijima KM. 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 Neurosci* 2019;20:13. DOI PubMed PMC
60. McGowan E, Eriksen J, Hutton M. A decade of modeling Alzheimer's disease in transgenic mice. *Trends Genet* 2006;22:281-9. DOI PubMed
61. Sasaguri H, Hashimoto S, Watamura N, et al. Recent advances in the modeling of Alzheimer's disease. *Front Neurosci* 2022;16:807473. DOI PubMed PMC
62. Flood DG, Lin YG, Lang DM, et al. A transgenic rat model of Alzheimer's disease with extracellular Abeta deposition. *Neurobiol Aging* 2009;30:1078-90. DOI PubMed
63. Elder GA, Gama Sosa MA, De Gasperi R, Dickstein DL, Hof PR. Presenilin transgenic mice as models of Alzheimer's disease. *Brain Struct Funct* 2010;214:127-43. DOI PubMed PMC
64. Leuzy A, Smith R, Ossenkoppele R, et al. Diagnostic performance of RO948 F 18 tau positron emission tomography in the differentiation of Alzheimer disease from other neurodegenerative disorders. *JAMA Neurol* 2020;77:955-65. DOI PubMed PMC
65. Götz J, Gladbach A, Pennanen L, et al. Animal models reveal role for tau phosphorylation in human disease. *Biochim Biophys Acta* 2010;1802:860-71. DOI PubMed
66. Eskandari-Sedighi G, Daude N, Gapeshina H, et al. The CNS in inbred transgenic models of 4-repeat Tauopathy develops consistent tau seeding capacity yet focal and diverse patterns of protein deposition. *Mol Neurodegener* 2017;12:72. DOI PubMed PMC
67. Myers A, McGonigle P. Overview of transgenic mouse models for Alzheimer's disease. *Curr Protoc Neurosci* 2019;89:e81. DOI PubMed
68. Esquerda-Canals G, Montoliu-Gaya L, Guell-Bosch J, Villegas S. Mouse models of Alzheimer's disease. *J Alzheimers Dis* 2017;57:1171-83. DOI PubMed
69. Kragh PM, Nielsen AL, Li J, et al. Hemizygous minipigs produced by random gene insertion and handmade cloning express the Alzheimer's disease-causing dominant mutation APPsw. *Transgenic Res* 2009;18:545-58. DOI PubMed
70. Jakobsen JE, Johansen MG, Schmidt M, et al. Generation of minipigs with targeted transgene insertion by recombinase-mediated cassette exchange (RMCE) and somatic cell nuclear transfer (SCNT). *Transgenic Res* 2013;22:709-23. DOI PubMed PMC
71. Søndergaard LV, Ladewig J, Dagnæs-Hansen F, Herskin MS, Holm IE. Object recognition as a measure of memory in 1-2 years old transgenic minipigs carrying the APPsw mutation for Alzheimer's disease. *Transgenic Res* 2012;21:1341-8. DOI PubMed
72. King A. The search for better animal models of Alzheimer's disease. *Nature* 2018;559:S13-5. DOI PubMed
73. Beckman D, Morrison JH. Towards developing a rhesus monkey model of early Alzheimer's disease focusing on women's health. *Am J Primatol* 2021;83:e23289. DOI PubMed
74. Heuer E, Rosen RF, Cintron A, Walker LC. Nonhuman primate models of Alzheimer-like cerebral proteopathy. *Curr Pharm Des* 2012;18:1159-69. DOI PubMed PMC
75. Paspalas CD, Carlyle BC, Leslie S, et al. The aged rhesus macaque manifests Braak stage III/IV Alzheimer's-like pathology. *Alzheimers Dement* 2018;14:680-91. DOI PubMed PMC
76. Arnsten AFT, Datta D, Leslie S, Yang ST, Wang M, Nairn AC. Alzheimer's-like pathology in aging rhesus macaques: unique opportunity to study the etiology and treatment of Alzheimer's disease. *Proc Natl Acad Sci U S A* ;2019:26230-8. DOI PubMed PMC
77. Arnsten AFT, Datta D, Preuss TM. Studies of aging nonhuman primates illuminate the etiology of early-stage Alzheimer's-like neuropathology: An evolutionary perspective. *Am J Primatol* 2021;83:e23254. DOI PubMed PMC
78. Yang M, Miao J, Rizak J, et al. Alzheimer's disease and methanol toxicity (part 2): lessons from four rhesus macaques (Macaca mulatta) chronically fed methanol. J Alzheimers Dis 2014;41(4):1131-47. DOI PubMed
79. Zhai R, Rizak J, Zheng N, et al. Alzheimer's disease-like pathologies and cognitive impairments induced by formaldehyde in non-human primates. *Curr Alzheimer Res* 2018;15:1304-21. DOI PubMed
80. Beckman D, Ott S, Donis-Cox K, et al. Oligomeric Aβ in the monkey brain impacts synaptic integrity and induces accelerated cortical aging. *Proc Natl Acad Sci U S A* ;2019:26239-46. DOI PubMed PMC
81. Forny-Germano L, Lyra e Silva NM, Batista AF, et al. Alzheimer's disease-like pathology induced by amyloid-β oligomers in nonhuman primates. *J Neurosci* 2014;34:13629-43. DOI PubMed PMC
82. Yue F, Feng S, Lu C, et al. Synthetic amyloid-β oligomers drive early pathological progression of Alzheimer's disease in nonhuman

primates. *iScience* 2021;24:103207. DOI PubMed PMC

83. Veitch DP, Weiner MW, Aisen PS, et al; Alzheimer's Disease Neuroimaging Initiative. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement* 2019;15:106-52. DOI PubMed
84. Iaccarino L, Tammewar G, Ayakta N, et al. Local and distant relationships between amyloid, tau and neurodegeneration in Alzheimer's Disease. *Neuroimage Clin* 2018;17:452-64. DOI PubMed PMC
85. Beckman D, Chakrabarty P, Ott S, et al. A novel tau-based rhesus monkey model of Alzheimer's pathogenesis. *Alzheimers Dement* 2021;17:933-45. DOI PubMed PMC
86. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet* 2021;397:2284-303. DOI PubMed
87. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA* 2020;323:548-60. DOI PubMed
88. Kordower JH, Olanow CW, Dodiya HB, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain* 2013;136:2419-31. DOI PubMed PMC
89. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. *Ageing Res Rev* 2018;42:72-85. DOI PubMed
90. Lee Y, Dawson VL, Dawson TM. Animal models of Parkinson's disease: vertebrate genetics. *Cold Spring Harb Perspect Med* 2012;2:a009324-a009324. DOI PubMed PMC
91. Teil M, Arotcarena ML, Dehay B. A new rise of non-human primate models of synucleinopathies. *Biomedicines* 2021;9:272. DOI PubMed PMC
92. Li H, Su LY, Yang L, et al. A cynomolgus monkey with naturally occurring Parkinson's disease. *Natl Sci Rev* 2021;8:nwaa292. DOI PubMed PMC
93. Porras G, Li Q, Bezard E. Modeling Parkinson's disease in primates: the MPTP model. *Cold Spring Harb Perspect Med* 2012;2:a009308. DOI PubMed PMC
94. Tieu K. A guide to neurotoxic animal models of Parkinson's disease. *Cold Spring Harb Perspect Med* 2011;1:a009316. DOI PubMed PMC
95. Lei X, Li H, Huang B, et al. 1-Methyl-4-phenylpyridinium stereotactic infusion completely and specifically ablated the nigrostriatal dopaminergic pathway in rhesus macaque. *PLoS One* 2015;10:e0127953. DOI PubMed PMC
96. Huang B, Wu S, Wang Z, et al. 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* 2018;379:302-15. DOI PubMed
97. Koprich JB, Johnston TH, Reyes G, Omana V, Brotchie JM. 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* 2016;11:e0167235. DOI PubMed PMC
98. Niu Y, Guo X, Chen Y, et al. Early Parkinson's disease symptoms in α-synuclein transgenic monkeys. *Hum Mol Genet* 2015;24:2308-17. DOI PubMed PMC
99. Yang W, Wang G, Wang CE, et al. Mutant alpha-synuclein causes age-dependent neuropathology in monkey brain. *J Neurosci* 2015;35:8345-58. DOI PubMed PMC
100. Blesa J, Przedborski S. Parkinson's disease: animal models and dopaminergic cell vulnerability. *Front Neuroanat* 2014;8:155. DOI PubMed PMC
101. Yang W, Liu Y, Tu Z, et al. CRISPR/Cas9-mediated PINK1 deletion leads to neurodegeneration in rhesus monkeys. *Cell Res* 2019;29:334-6. DOI PubMed PMC
102. Chen ZZ, Wang JY, Kang Y, et al. PINK1 gene mutation by pair truncated sgRNA/Cas9-D10A in cynomolgus monkeys. *Zool Res* 2021;42:469-77. DOI PubMed PMC
103. Yang W, Guo X, Tu Z, et al. PINK1 kinase dysfunction triggers neurodegeneration in the primate brain without impacting mitochondrial homeostasis. *Protein Cell* 2022;13:26-46. DOI PubMed PMC
104. Yang W, Li S, Li XJ. A CRISPR monkey model unravels a unique function of PINK1 in primate brains. *Mol Neurodegener* 2019;14:17. DOI PubMed PMC
105. Li H, Wu S, Ma X, et al. Co-editing PINK1 and DJ-1 genes via adeno-associated virus-delivered CRISPR/Cas9 system in adult monkey brain elicits classical parkinsonian phenotype. *Neurosci Bull* 2021;37:1271-88. DOI PubMed PMC
106. Grad LI, Rouleau GA, Ravits J, Cashman NR. Clinical spectrum of amyotrophic lateral sclerosis (ALS). *Cold Spring Harb Perspect Med* 2017;7:a024117. DOI PubMed PMC
107. Talbott EO, Malek AM, Lacomis D. The epidemiology of amyotrophic lateral sclerosis. *Handb Clin Neurol* 2016;138:225-38. DOI PubMed
108. Forman MS, Trojanowski JQ, Lee VM. TDP-43: a novel neurodegenerative proteinopathy. *Curr Opin Neurobiol* 2007;17:548-55. DOI PubMed PMC
109. Saberi S, Stauffer JE, Schulte DJ, Ravits J. Neuropathology of amyotrophic lateral sclerosis and its variants. *Neurol Clin* 2015;33:855-76. DOI PubMed PMC
110. Lagier-Tourenne C, Cleveland DW. Rethinking ALS: the FUS about TDP-43. *Cell* 2009;136:1001-4. DOI PubMed PMC
111. Cruz S, Cleveland DW. Understanding the role of TDP-43 and FUS/TLS in ALS and beyond. *Curr Opin Neurobiol* 2011;21:904-19. DOI PubMed PMC
112. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314:130-3. DOI PubMed

113. Chen-Plotkin AS, Lee VM, Trojanowski JQ. TAR DNA-binding protein 43 in neurodegenerative disease. *Nat Rev Neurol* 2010;6:211-20. DOI PubMed PMC
114. Mitchell JC, Constable R, So E, et al. Wild type human TDP-43 potentiates ALS-linked mutant TDP-43 driven progressive motor and cortical neuron degeneration with pathological features of ALS. *Acta Neuropathol Commun* 2015;3:36. DOI PubMed PMC
115. Wang G, Yang H, Yan S, et al. Cytoplasmic mislocalization of RNA splicing factors and aberrant neuronal gene splicing in TDP-43 transgenic pig brain. *Mol Neurodegener* 2015;10:42. DOI PubMed PMC
116. Huang C, Tong J, Bi F, Zhou H, Xia XG. Mutant TDP-43 in motor neurons promotes the onset and progression of ALS in rats. *J Clin Invest* 2012;122:107-18. DOI PubMed PMC
117. Shan X, Chiang PM, Price DL, Wong PC. Altered distributions of Gemini of coiled bodies and mitochondria in motor neurons of TDP-43 transgenic mice. *Proc Natl Acad Sci U S A* 2010;107:16325-30. DOI PubMed PMC
118. Wils H, Kleinberger G, Janssens J, et al. TDP-43 transgenic mice develop spastic paralysis and neuronal inclusions characteristic of ALS and frontotemporal lobar degeneration. *Proc Natl Acad Sci U S A* 2010;107:3858-63. DOI PubMed PMC
119. Yin P, Guo X, Yang W, et al. Caspase-4 mediates cytoplasmic accumulation of TDP-43 in the primate brains. *Acta Neuropathol* 2019;137:919-37. DOI PubMed PMC
120. Uchida A, Sasaguri H, Kimura N, et al. Non-human primate model of amyotrophic lateral sclerosis with cytoplasmic mislocalization of TDP-43. *Brain* 2012;135:833-46. DOI PubMed PMC
121. Yang H, Yang S, Jing L, et al. Truncation of mutant huntingtin in knock-in mice demonstrates exon1 huntingtin is a key pathogenic form. *Nat Commun* 2020;11:2582. DOI PubMed PMC
122. Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. *Nat Rev Dis Primers* 2015;1:15005. DOI PubMed
123. Farshim PP, Bates GP. Mouse models of Huntington's disease. *Methods Mol Biol* 2018;1780:97-120. DOI PubMed
124. Lee H, Heiman M. Back-to-BACs in Huntington's disease modeling. *Neuron* 2022;110:1087-9. DOI PubMed
125. Yang SH, Cheng PH, Banta H, et al. Towards a transgenic model of Huntington's disease in a non-human primate. *Nature* 2008;453:921-4. DOI PubMed PMC
126. Yang SH, Cheng PH, Sullivan RT, Thomas JW, Chan AW. Lentiviral integration preferences in transgenic mice. *Genesis* 2008;46:711-8. DOI PubMed PMC
127. Putkhao K, Kocerha J, Cho IK, Yang J, Parnpai R, Chan AW. Pathogenic cellular phenotypes are germline transmissible in a transgenic primate model of Huntington's disease. *Stem Cells Dev* 2013;22:1198-205. DOI PubMed PMC
128. Moran S, Chi T, Prucha MS, et al. Germline transmission in transgenic Huntington's disease monkeys. *Theriogenology* 2015;84:277-85. DOI PubMed PMC
129. Khampang S, Parnpai R, Mahikul W, Easley CA 4th, Cho IK, Chan AWS. CAG repeat instability in embryonic stem cells and derivative spermatogenic cells of transgenic Huntington's disease monkey. *J Assist Reprod Genet* 2021;38:1215-29. DOI PubMed PMC
130. Kocerha J, Liu Y, Willoughby D, et al. Longitudinal transcriptomic dysregulation in the peripheral blood of transgenic Huntington's disease monkeys. *BMC Neurosci* 2013;14:88. DOI PubMed PMC
131. Chan AW, Xu Y, Jiang J, et al. A two years longitudinal study of a transgenic Huntington disease monkey. *BMC Neurosci* 2014;15:36. DOI PubMed PMC
132. Yang D, Wang CE, Zhao B, et al. Expression of Huntington's disease protein results in apoptotic neurons in the brains of cloned transgenic pigs. *Hum Mol Genet* 2010;19:3983-94. DOI PubMed PMC
133. Baxa M, Hruska-Plochan M, Juhas S, et al. A transgenic minipig model of Huntington's Disease. *J Huntingtons Dis* 2013;2:47-68. DOI PubMed
134. Schuldenzucker V, Schubert R, Muratori LM, et al. Behavioral testing of minipigs transgenic for the Huntington gene-A three-year observational study. *PLoS One* 2017;12:e0185970. DOI PubMed PMC
135. Yan S, Tu Z, Liu Z, et al. A Huntingtin knockin pig model recapitulates features of selective neurodegeneration in Huntington's disease. *Cell* 2018;173:989-1002.e13. DOI PubMed PMC
136. Meng L, Ely JJ, Stouffer RL, Wolf DP. Rhesus monkeys produced by nuclear transfer. *Biol Reprod* 1997;57:454-9. DOI PubMed
137. Liu Z, Cai Y, Wang Y, et al. Cloning of macaque monkeys by somatic cell nuclear transfer. *Cell* 2018;172:881-887.e7. DOI PubMed
138. Liu Z, Cai Y, Liao Z, et al. Cloning of a gene-edited macaque monkey by somatic cell nuclear transfer. *Natl Sci Rev* 2019;6:101-8. DOI PubMed PMC
139. Yeh WH, Shubina-Oleinik O, Levy JM, et al. In vivo base editing restores sensory transduction and transiently improves auditory function in a mouse model of recessive deafness. *Sci Transl Med* 2020;12:eaay9101. DOI PubMed PMC
140. Yang L, Yang B, Chen J. One prime for all editing. *Cell* 2019;179:1448-50. DOI PubMed
141. Mazid MA, Ward C, Luo Z, et al. Rolling back human pluripotent stem cells to an eight-cell embryo-like stage. *Nature* 2022;605:315-24. DOI PubMed
142. Yin P, Tu Z, Yin A, et al. Aged monkey brains reveal the role of ubiquitin-conjugating enzyme UBE2N in the synaptosomal accumulation of mutant huntingtin. *Hum Mol Genet* 2015;24:1350-62. DOI PubMed PMC