Review

Patient-Specific iPSCs-Based Models of Neurodegenerative Diseases: Focus on Aberrant Calcium Signaling

Dmitriy A. Grekhnev, Elena V. Kaznacheyeva and Vladimir A. Vigont

Laboratory of Ionic Channels of Cell Membranes, Department of Molecular Physiology of the Cell, Institute of Cytology, Russian Academy of Sciences, 4 Tikhoretsky Ave., 194064 St. Petersburg, Russia; dima.grehnyov@yandex.ru (D.A.G.); evkazn@incras.ru (E.V.K.)

* Correspondence: vvigand@gmail.com

Abstract: The development of cell reprogramming technologies became a breakthrough in the creation of new models of human diseases, including neurodegenerative pathologies. The iPSCs-based models allow for the studying of both hereditary and sporadic cases of pathologies and produce deep insight into the molecular mechanisms underlying neurodegeneration. The use of the cells most vulnerable to a particular pathology makes it possible to identify specific pathological mechanisms and greatly facilitates the task of selecting the most effective drugs. To date, a large number of studies on patient-specific models of neurodegenerative diseases has been accumulated. In this review, we focused on the alterations of such a ubiquitous and important intracellular regulatory pathway as calcium signaling. Here, we reviewed and analyzed the data obtained from iPSCs-based models of different neurodegenerative disorders that demonstrated aberrant calcium signaling.

Keywords: patient-specific models; calcium signaling; Alzheimer’s disease; Parkinson’s disease; Huntington’s disease; spinocerebellar ataxia; amyotrophic lateral sclerosis; induced pluripotent stem cells; iPSCs; neurodegeneration

1. Introduction

Neurodegenerative diseases are one of the most socially significant problems facing modern medicine. The number of people suffering from neurodegenerative pathologies is growing every year. According to data from the World Health Organization, more than 55 million people live with dementia (predominantly Alzheimer’s disease) worldwide, and there are nearly 10 million new cases every year. As the proportion of older people in the population is increasing in most countries, this number is expected to rise to 78 million in 2030 and 139 million in 2050 [1]. Parkinson’s disease (PD) is the second most frequent neurodegenerative pathology. Over recent decades, the number of people suffering from PD has more than doubled to over 6 million. Of all the neurological disorders, PD has increased at the fastest rate [2]. The progression of dementia leads to the disability of patients and requires colossal expenses for their medical support. Thus, the development of new approaches to treating neurodegenerative diseases remains highly relevant. Unfortunately, most of the existing methods of therapy are aimed at symptomatic treatment and do not address the basic causes of the pathologies. Therefore, one of the most important tasks of modern neuroscience is to study the molecular mechanisms underlying neurodegeneration and search for new targets for the treatment of neurodegenerative pathologies. To solve this important issue, the development of adequate models reflecting, as accurately as possible, the pathological processes of a particular disease is required. The discovery of induced pluripotency [3] and the improvement of protocols for stem cell differentiation was a real breakthrough along this path. The main advantages of models based on patient-specific induced pluripotent stem cells (iPSCs) are the endogenous expression of mutant genes and the possibility of studying the sporadic cases of diseases. Moreover, the targeted...
differentiation into different types of neurons including highly vulnerable and commonly protected neurons makes it possible to study the molecular basis of selective neuronal death.

The previously proposed calcium hypothesis of neurodegeneration [4] postulates that the main factor triggering neurodegenerative processes in neurons is a disturbance of intracellular calcium signaling. Indeed, impaired calcium homeostasis has been reported for a wide range of neurodegenerative diseases, in both cellular and animal model studies [5–10]. In this review, we have summarized the data accumulated to date on established iPSCs-based models of various neurodegenerative pathologies, focusing on the revealed changes in calcium signaling.

2. Problems and Prospects of iPSCs-Based Models of Neurodegenerative Diseases

The era of cell differentiation began with the production and culturing of embryonic stem cells (ESCs) [11,12]. These cells have pluripotent properties and can be differentiated into any type of adult cells. With the development of differentiation protocols, the use of ESCs has become widespread for modeling neurodegenerative pathologies, including Alzheimer’s disease (AD) [13–15], Parkinson’s disease (PD) [16–18], Huntington’s disease (HD) [19,20], spinocerebellar ataxias (SCA) [21], amyotrophic lateral sclerosis (ALS) [22–24], and other neurological disorders [25]. However, the use of human ESCs is limited by access to preimplantation embryos and the associated ethical issues. Therefore, to model pathologies recently, ESCs of model animals are mainly used.

The discovery of induced pluripotency by Professor Yamanaka created a new impulse in disease modeling using genetic reprogramming of the cells. It was postulated that the expression of only four transcription factors (Oct-4, Sox2, c-Myc, Klf4) can return a differentiated cell to the pluripotent state [3]. Those cells were called iPSCs. Numerous studies showed that iPSCs are fundamentally no different from ESCs: they can be maintained in culture and can potentially be differentiated into any type of somatic cell. However, some differences can be observed in the pattern of DNA methylation and gene expression [26–28]. An important advantage of iPSCs has been the elimination of many ethical problems associated with obtaining ESCs. The main applications of human iPSCs are the establishing of cellular models of diseases and also regenerative medicine and drug testing (Figure 1).

![Figure 1. iPSCs in modeling neurodegenerative diseases, drug screening, and cell therapy.](image)

Model iPSCs lines obtained through the genetic reprogramming of a patient’s biological material are called patient-specific models. They reflect the pathological phenotype of a patient with this disease. The key advantage of iPSCs-based models is the endogenous expression of mutant genes, which makes it possible to assess the expression levels of affected genes, as well as to study the pathophysiological mechanisms under “native” conditions. Another important advantage of iPSCs-based models is the possibility of iPSCs
to be differentiated into the cell type that is most vulnerable in this particular disease. In particular, it can be expected that the use of iPSCs-based models will shed light on one of the key problems of neurodegeneration—the causes of selective neuronal death.

In medical practice, the use of iPSCs creates tremendous opportunities for personalized therapy, as for each person, iPSCs from their own differentiated cells can be obtained. Subsequent genetic correction of the mutant allele and differentiation of iPSCs into cell preparations will allow for transplantation treatment. However, this approach has serious limitations due to the increased risk of tumor formation even in the case of autologous transplantation. Nevertheless, the developed cerebral organoids represent a promising transplantation source. Transplanted rat cerebral organoids demonstrate multilineage differentiation and migration in different damaged brain areas [29]. At the same time, another application of iPSCs as a platform for screening potential drugs remains highly relevant. Also, the recent advances in applying the use of high-throughput screening, computer-aided drug design, and the development of microfluidic blood–brain barrier models can significantly improve drug selection efficiency and complement iPSCs-based drug screening systems [30–35].

Drug development is very expensive but approximately 90% of drugs in human clinical trials are discarded and never sold. The main reasons for this high failure rate are lack of efficacy and existing limitations in human disease models and drug safety testing. The iPSCs-based models provide a unique opportunity for drug discovery and testing, as they enable the considering of cellular and, in particular, neuronal specificity while the activity of potential drug compounds is tested. This is highly important for the screening of neuroprotective compounds because neurodegenerative pathologies are often characterized by selective neuronal death. For example, the predominant death of striatal medium spiny neurons was detected in Huntington’s disease, whereas the most vulnerable neuronal types in Parkinson’s disease and amyotrophic lateral sclerosis are dopaminergic neurons and motor neurons, consequently. Thus, testing a drug on neurons without considering the specificity of neuronal vulnerability can significantly limit the search for effective compounds. It is expected that small molecules selected using iPSCs-based models will demonstrate similar efficacy in the treatment of patients. During the screening of chemicals, in addition to their effectiveness, their toxicity is checked. Appropriate screening using iPSCs-based models to select highly potent, low toxicity chemicals would significantly reduce drug development costs.

Despite the many advantages of using patient-specific models, challenges exist. First is the problem of genetic heterogeneity between different patients and between control and disease. Significant variations in the pathological phenotype are often observed even for patients with monogenic diseases with the same mutation. Therefore, it is important to consider the influence of other genes. To overcome this limitation, isogenic cell lines were established, differing only by a mutation in a particular gene [36–45].

Another important limitation is the fact that in vitro differentiation is different from the physiological maturation of cells in the organism. Therefore, although the iPSCs-based models can be considered among the most successful and physiologically adequate models of neurodegenerative pathologies, scientists strive to make these models even more relevant, developing, in particular, strategies for three-dimensional cultivation of cell structures similar to a primitive brain [46–49].

3. Obtaining the iPSCs-Based Models of Neurodegenerative Diseases

The creation of a patient-specific iPSCs-based model of the disease begins with the search for a patient with the corresponding pathology. Medical neurological centers diagnose the disease and collect biological material from donors (skin biopsy or peripheric blood sampling), who have previously signed an informed consent. Further, a fibroblast culture is obtained from the collected biological material of the patient. The next step is the return of cells to the pluripotent state (reprogramming of the fibroblast culture into iPSCs). Some models stop at this stage [50]. For the other models, the final stage is a
differentiation of iPSCs into the suitable cell type, as a rule, into the most vulnerable in this pathology (Figure 1). It is important to find out at what stage of differentiation the pathological phenotype is reproduced. It has been shown that terminally differentiated cells more fully reflect the disease phenotype than do iPSCs or NPCs (neuronal progenitor cells) for many neurodegenerative pathologies [41,51,52].

The patient-specific models can be obtained by both reprogramming cells in iPSCs and their subsequent differentiation, and direct induction of somatic cells (Figure 1). Direct induction can be induced by overexpression of a set of transcription factors that promote chromatin remodeling and trigger direct cell differentiation, bypassing the stage of iPSCs generation [53–57].

Cell reprogramming into iPSCs is triggered by transcription factors that return a differentiated cell to a pluripotent state. To deliver genes encoding these factors into cells, the retroviruses (in particular, lentivirus) can be used to integrate the required genes into the host genome [8,58], and Sendai (non-integrative) viruses or transient transfection [59,60]. Both methods of reprogramming have similar efficiency, and the cell models obtained by these methods, as a rule, do not have any morphological or functional differences [61]. The use of the Sendai virus looks more promising, as the virus plasmid does not integrate into the cell genome, removing the risk of protooncogene activation, which may occur during an integrative lentiviral infection.

The differentiation process includes three principal stages: neuronal induction, the production of cells of the lateral ganglionic eminence (LGE), and terminal differentiation. Obtaining the required type of neurons is necessary to choosing the appropriate combination (and concentration) of cell proliferation and differentiation factors that best suits the conditions in the developing brain.

The process of establishing the iPSCs-based models of the diseases at all stages is accompanied by the careful characterization of the obtained cells. This includes confirmation of the presence or absence of specific markers, testing the ability of iPSCs to differentiate into cells of all three germ layers, and testing for teratoma formation. Karyotyping is performed to control chromosomal rearrangements that periodically occur during reprogramming and cell culture. Using the methods of immunocytochemistry and PCR, the expression of specific protein markers is analyzed: pluripotency (TRA-1-60, TRA-1-81, SSEA-3, SSEA4, Oct-4), germ layers (PAX6, SOX1 (ectoderm), GATA4, α-SMA (mesoderm), SOX17, AFP (endoderm), and differentiated cells such as neurons (MAP2, NCAM, Tuj1, DCX). In addition, morphological and functional control of the resulting cells is required. Functional confirmation of successful neuronal differentiation can include a demonstration of the ability to respond to depolarization of the plasma membrane, generation of action potentials, and forming synapses and specific morphological structures characterizing the particular neuronal type (such as spines for medium spiny neurons). When hereditary pathology is modeled, it is also necessary to confirm the presence of the mutation.

Since the first publication in 2007, describing a protocol for generating iPSCs from human somatic cells, there has been an explosion in methods of differentiation into various types of cells, including neurons. Protocols for differentiation into multiple subtypes of neurons [58,62–64], as well as astrocytes [65,66], microglia [67–69], oligodendrocytes [70], and endothelial cells [71,72], have been developed. Improved differentiation protocols continue to increase the yield, purity, and maturity of cells.

To date, it is known that various neurodegenerative diseases, including AD, PD, and HD, are characterized by impairments in different types of cells (neurons, astrocytes, oligodendrocytes, microglia, pericytes, and endothelial cells); therefore, three-dimensional (3D) and co-culture models are required to reproduce those pathology mechanisms that cannot be detected in monocultures or two-dimensional cultures [36,69,73]. This is quite important because the expression of key genes and proteins in glial cells has been proven to be varied between 2D and 3D cultures [29].
The existing iPSCs-based models already represent an important instrument for basic science studies and the search for new drugs. However, these models must be improved to obtain more precise modeling of the pathogenesis of the diseases.

4. Neurodegeneration and Calcium Signaling

Calcium is one of the most ubiquitous secondary messengers in the cell. Calcium signaling controls a wide range of important intracellular processes such as gene expression, proliferation, and apoptosis. The key “players” that regulate the concentration of free calcium ions in the cell include the endoplasmic (sarcoplasmic) reticulum [74], mitochondria [74,75], lysosomes [76], calcium-binding proteins [77], and ion transporters: calcium-permeable ion channels [74,78], calcium ATPases [79,80], and exchangers [81,82]. It should also be noted that mitochondrial dysfunction is closely related to aberrant calcium signaling, as mitochondria are stores of calcium in cells, and excessive calcium uptake can lead to mitochondria overload, caspase activation, and apoptosis. The major organelles that maintain calcium homeostasis in cell mitochondria and the ER also play a critical role in oxidative stress [74,75], neuroinflammation [83,84], and apoptosis [84]. Thus, alterations in the production of reactive oxygen species that can lead to ER stress should also be addressed in studies of aberrant calcium signaling.

Disturbances in various components of calcium signaling are widely spread in different pathologies, including neurodegenerative diseases [85–88]. For the first time, the calcium hypothesis of neurodegeneration was proposed by neuroscientist Zaven Khachaturian in 1982 and published in 1984 [4]. The author noted the correlation between the disturbance of calcium homeostasis in the aging brain and the occurrence of age-related neurodegenerative pathologies such as Alzheimer’s disease. In 1994, an updated version of the calcium hypothesis “Calcium hypothesis of Alzheimer’s disease and brain aging” was published, clarifying the molecular mechanisms of calcium homeostasis disturbance [89]. Later, in 2004, the calcium hypothesis for Huntington’s disease was formulated [90]. In 2009, Professor Bezprozvanny summarized the results demonstrating impaired calcium signaling in AD, PD, HD, ALS, and SCAs [85]. Nevertheless, the lack of specific drugs with proven therapeutic effects, including calcium signaling modulators [91], makes the search for new targets and compounds highly relevant. This requires further study of the molecular mechanisms of neurodegeneration, within both the framework of the calcium hypothesis and its alternatives.

To date, a great deal of data has been accumulated on disturbances in calcium signaling in different models of neurodegenerative disorders including animal and cellular models. In the last decade, the patient-specific models of neurodegenerative diseases have created new opportunities in studying the pathogenesis of these pathologies and clarifying the calcium hypothesis of neurodegeneration. Here, we systematized the data on pathological calcium signaling in iPSCs-based models of neurodegenerative diseases.

5. Alzheimer’s Disease

Alzheimer’s disease (AD) is one of the most widespread neurodegenerative disorders, characterized by the predominant death of neurons in the hippocampus, cerebral cortex, and locus coeruleus [92–95]. The neuropathological hallmarks of AD are amyloid aggregates, hyperphosphorylation of the tau protein, and neurofibrillary tangles [92,96]. Hereditary AD cases are caused mostly by mutations in the genes PSEN1 and PSEN2, encoding presenilin proteins, and APP, encoding the β-amyloid precursor protein.

The first iPSCs-based AD neuronal model was performed in 2011 [97]. Further, the isogenic models were created [37–39,98]. Currently studied AD cellular models are 3D iPSCs-based neurons [46,48,99] and 2D cell cultures [37,97,100–104] including cortical neurons [105,106] and cholinergic neurons [107] as well as astrocytes [105,108], microglia [67,69], and endothelial cells [72,109] (Table 1).
In iPSCs-based models of familiar AD, an increase in the production of reactive oxygen species, impaired energy status and mitochondrial potential, lysosomal acidification, impaired autophagy and mitophagy, and aberrant calcium signaling have been shown [99,104]. The release of calcium by mitochondria and the endoplasmic reticulum plays an important role in the transmission of calcium signals in various cells. In PSEN1-associated AD, these pathways are disrupted, which may cause a further imbalance in calcium homeostasis (and contribute to AD pathogenesis). In particular, an increase in the rate of calcium leakage from the ER in astrocytes modeling AD has been shown [108]. It has also been reported that calcium release from the ER is enhanced in patient-specific AD neurons [104]. Moreover, inhibition of the key mitochondrial enzymatic complex alpha-ketoglutarate dehydrogenase resulted in the restoration of calcium reserves in the ER. These effects were observed in terminally differentiated neurons and were absent in iPSCs and NPCs [104].

In addition to hereditary forms of AD, genetic reprogramming technologies make it possible to study sporadic cases of the disease. In iPSCs-based models of sporadic AD, a mitochondrial dysfunction and an increase in both the production of reactive oxygen species and the number of complexes of the respiratory chain have been shown [103].

AD-specific astrocytes were also characterized by the occurrence of stress in the endoplasmic reticulum [105] and increased production of reactive oxygen species [105,108]. Also, astrocytes form the glymphatic pathway, which plays an important role in AD [110–113]. It is a waste clearance system that utilizes a unique system of perivascular channels, formed by astroglial cells, to promote the efficient elimination of soluble proteins and metabolites from the central nervous system. Intriguing data demonstrating that targeting calcium–calmodulin signaling mechanisms in astrocytes is a viable therapeutic option was obtained by Dr. Kitchen [114]. That study showed that pharmacological inhibition of calcium–calmodulin signaling events prevented the development of CNS edema and

### Table 1. Alterations in calcium signaling in iPSCs-based models of Alzheimer’s disease.

| Mutant genes | Cell type | Disturbance associated with calcium signaling | Reference |
|--------------|-----------|---------------------------------------------|-----------|
| PSEN1        | Neurons   | Increased ROS production, impaired energy status and mitochondrial potential, impaired autophagy and mitophagy, and increased calcium release from the ER | [104]     |
|              | Astrocytes| Disturbed calcium release from the ER, increased ROS production | [108]     |
| PSEN2        | Neurons   | Increased amplitude of spontaneous calcium oscillations and their desynchronization, hyperactivation of neurons | [99]      |
| APP          | Astrocytes| ER stress, increased ROS production | [105]     |
| Sporadic forms | Neurons | Mitochondrial dysfunction, increased ROS production, increased levels of oxidative phosphorylation chain complexes | [103]     |
promoted functional recovery in injured rats. This role has been recently confirmed by work demonstrating that astrocytes are a viable therapeutic target using a photothrombotic stroke model [115].

6. Parkinson’s Disease

Parkinson’s disease (PD) is the second most common neurodegenerative disorder. The main pathophysiological feature of PD is the progressive death of dopaminergic neurons in the substantia nigra [116]. Pathological mechanisms of PD (Table 2) were studied using many iPSCs-based models, including neuroepithelial stem cells (NESC) [117], dopaminergic neurons [51,118–136], cortical neurons [137], and astrocytes [66] and microglia [68]. Isogenic models of PD are also widely used [41,43,45]. iPSCs-based models were obtained mainly from patients carrying mutations in genes encoding α-synuclein (SNCA), leucine repeat-rich kinase 2 (LRRK2), PTEN-induced kinase 1 (PINK1), ubiquitin ligase (E3) parkin (PARK2), a regulator of intracellular protein sorting (VPS35), and β-glucocerebrosidase (GBA).

Table 2. Alterations in calcium signaling in iPSCs-based models of Parkinson’s disease.

| Parkinson’s Disease | iPSCs-based models |
|---------------------|---------------------|
| The most vulnerable areas of the brain | Patient-specific models |
| NESC | [117] |
| Dopaminergic neurons (DAn) | [51,118–136,138] |
| Cortical neurons | [137] |
| Astrocytes | [66] |
| Microglia | [68] |
| Isogenic models | |
| DAn | [41,45] |
| Cortical neurons | [43] |

Mutant genes | Cell type | Disturbance associated with calcium signaling |
|--------------|-----------|---------------------------------------------|
| NESC | Mitochondrial dysfunction, impaired mitophagy | [117] |
| LRRK2 | DAn | Enhanced expression of genes involved in calcium signaling, as well as an increase in calcium influx, mitochondrial dysfunction, mitochondrial DNA damage, oxidative stress, disrupted calcium dynamics in the ER | [120,121,124,125,127,131,132,136,138] |
| SNCA | Cortical neurons | Mitochondrial dysfunction, oxidative stress | [137] |
| | DAn | Mitochondrial dysfunction, ER stress, impaired calcium homeostasis and ATP production | [43,119,130,131,135,139] |
| PINK1 | DAn | Mitochondrial dysfunction, oxidative stress, slowed utilization of damaged mitochondria | [133] |
| PARK2 | DAn | Mitochondrial dysfunction, oxidative stress, dysfunction of voltage-gated T-type calcium channels | [41,51,134,140] |
| DJ-1 | DAn | Oxidative stress | [129] |

In 1997, mutations in the SNCA gene were first identified as a trigger contributing to the manifestation of PD. Transcriptomic analysis of patient-specific dopaminergic neurons with mutations in SNCA showed impaired expression of genes associated with mitochondrial functioning [135]. Mitochondrial dysfunction not only has been identified on the gene level but also confirmed by functional assessment [43,119,131,137]. Morphological changes and decreased mitochondrial membrane potential were demonstrated [135,139]. Mutant α-synuclein disrupts the association of the endoplasmic reticulum and mitochondria,
which leads to endoplasmic reticulum stress and impaired calcium homeostasis and ATP production [130,135].

Mutations in the LRRK2 gene are among the most frequent causes of hereditary PD [141]. The most common G2019S mutation in LRRK2 has been studied in iPSCs-derived neurons [142]. LRRK2 plays a critical role in delayed mitophagy that leads to the accumulation of aberrant mitochondria [117,127]. An increased number of mitochondria with abnormal morphology, impaired functionality, and decreased membrane potential was detected in LRRK2 mutant cells by Professor Walter’s group [117]. PD iPSCs-based models also revealed the progression of oxidative stress [120,121], damage of mitochondrial DNA, and energy imbalance [132]. The crucial role of mitochondrial impairments in PD pathogenesis was confirmed by experiments demonstrating a neuroprotective effect of coenzyme Q10, rapamycin, and the LRRK2 inhibitor GW5074 [121].

Different effects of the mutation in LRRK2 on calcium dynamics in the endoplasmic reticulum have been obtained on iPSCs-based PD models [138]. It has been shown that incubation of dopaminergic neurons carrying the LRRK2 G2019S mutation with thapsigargin (a blocker of SERCA) leads to a decrease in the length of neurites. This effect was not observed in healthy control iPSCs-derived neurons [138]. The SERCA inhibition-dependent neurite collapse has been confirmed in isogenic models [138]. Finally, LRRK2 G2019S neurons were exposed to LRRK2 inhibitor MLi-2, as well as the use of antisense oligonucleotides that reduce LRRK2 expression (targeting the mRNA of the LRRK2 and preventing its translation) restore the neurite length in LRRK2 G2019S dopaminergic neurons [138]. It has also been reported that LRRK2 G2019S dopaminergic neurons incubated with thapsigargin showed a reduced calcium level in the endoplasmic reticulum, but an increased amount of calcium in the cytosol. In addition, there was an increased calcium uptake during depolarization [138]. The investigated pathological changes in calcium signaling could be restored by antisense oligonucleotides to LRRK2. It is important to note that the dynamics of calcium in the endoplasmic reticulum is one of the key factors in the regulation of store-operated calcium entry. A decrease in the concentration of calcium in the endoplasmic reticulum leads to the activation of STIM proteins, which activate store-operated calcium channels. Although authors note a decrease in the expression of some genes (STIM1, TRPC1, and ORA1) responsible for the machinery of the store-operated calcium entry [138], its functional changes have not been studied yet what might be interesting for future investigations. iPSCs-based neurons with mutations in the PINK1 and PAR2 genes showed several types of mitochondrial dysfunction such as aberrant morphology, increased ROS levels, oxidative stress, decreased mitochondrial respiration, and impaired mitochondrial motility [41,51,133,134]. Notably, the mitochondrial dysfunctions were detected in differentiated neurons and absent in the fibroblast cultures and iPSCs obtained from patients with these mutations [41,51]. Mutations in the Dj-1 gene are a rare cause of hereditary PD. Dopaminergic neurons with mutant Dj-1 show mitochondrial dysfunction that leads to the accumulation of oxidized dopamine in PD, which could be prevented by the calcineurin inhibitor FK506 [129]. Thus, impaired calcium signaling may significantly contribute to dopamine metabolism. In addition to mitochondrial dysfunction, the functioning of voltage-gated L-, R-, T-, N-, and P/Q-type channels in PD is currently being discussed [140,143,144]. It was found that mRNA, which has a complex secondary structure in the 5'-untranslated region (UTR), is translated more efficiently in neurons with the G2019S mutation in LRRK2. This leads to increased expression of many genes involved in the regulation of calcium signaling, including voltage-gated calcium channel (VGCC) subunits, and consequently results in the greater calcium influx and intracellular calcium concentration. [136]. iPSCs-derived neurons with the LRRK2 G2019S mutation also showed changes in neurite morphology and decreased calcium response under membrane depolarization conditions [125]. Impaired calcium signaling plays an important role in PD pathogenesis, which can be confirmed by the neuroprotective effects of small molecules and genetic approaches affecting calcium homeostasis machinery. For example, dopaminergic neurons obtained from a patient with a mutation in the PARK2 gene were rescued from the rotenone-induced apoptosis by both
the application of a VGCC antagonist benidipine and the knockdown of T-type calcium channels, thus demonstrating the involvement of voltage-gated calcium channels in PD pathology [140].

While most therapeutic strategies aim to prevent neuronal loss or protect vulnerable neurons, a potential alternative is to replace lost neurons to recover the neuronal network. A significant breakthrough was made by an article whose authors demonstrated the conversion of midbrain astrocytes to dopaminergic neurons, which provide axons to reconstruct the nigrostriatal circuit [145]. These data create new possibilities for the treatment of neurodegenerative diseases by replacing lost neurons.

7. Huntington’s Disease

Huntington’s disease (HD) is one of the inherited polyglutamine neurodegenerative disorders. In addition to HD, there are six types of spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17), dentatorubral-pallidoluysian atrophy (DRPLA), and spinal and bulbar muscular atrophy (SBMA)/Kennedy’s disease [146]. These pathologies are associated with the apathogenic expansion of glutamine-encoding (CAG) repeats in the mutant genes, which leads to the production of mutant proteins containing an abnormally elongated polyQ tract. Huntington’s disease occurs when the number of CAG repeats in the huntingtin gene exceeds 35 [146]. The hallmark of the pathology is the aggregation of mutant huntingtin (mHTT). Furthermore, impairments in intracellular transport, autophagy, gene expression, calcium homeostasis, energy imbalance, and oxidative stress were reported in HD [147–149]. Interestingly, mHTT production is ubiquitous in human tissues, but HD is characterized by a unique pattern of neuronal death. The most remarkable changes found in HD are a selective loss of GABAergic striatal medium spiny neurons (MSNs), severe atrophy of the caudate nucleus and putamen, and atrophy of cortical neurons [150].

For the first time, iPSCs from a patient with HD were characterized in 2008 [151]. Later, differentiated neurons were obtained [152]. To use the iPSCs-based models correctly, it is necessary to know the stage of differentiation and maturity of cells when changes occur. The pronounced differences in gene expression between patient-specific NPC and isogenic control and the absence of such differences between HD-specific iPSCs and isogenic control have been reported [52]. In 2012, the HD iPSCs Consortium announced the creation and characterization of a panel of 14 iPSCs lines from HD patients and healthy donors [153]. The first iPSCs-based 3D model of HD was presented in 2018 [49]. Currently, iPSCs-based HD models with terminal differentiation into cortical [154] and GABAergic neurons [8,61,155–158], astrocytes [159,160], endothelial cells [71], and isogenic models [36,44] are studied (Table 3).

Transcriptome analysis of iPSCs-based HD models showed a lower expression of the genes involved in calcium signaling, including the genes that encode for NMDA and AMPA glutamate receptors, nicotinic acetylcholine receptor subunits, some voltage-gated calcium channel subunits, plasma membrane calcium ATPases, and various effectors such as calcium–calmodulin dependent protein kinase (CAMKII), CALM, and CREB [73]. Also, the expression of genes responsible for cell death was impaired [50]. Suppression of the gene expression encoding proteins involved in the metabolism and signal transduction pathways of glutamate and GABA was also noted [73]. On the other hand, increased expression of genes encoding store-operated calcium channels and the inositol triphosphate receptor was noted [73]. Functionally, increased store-operated calcium entry was observed in differentiated GABAergic MSNs in adult-onset [8,157] and juvenile HD models [61]. We showed that STIM2, as a key activator of store-operated calcium channels in neurons, may play a critical role in increased store-operated calcium entry in HD and be a target for potential HD drugs [61]. In addition, we noted increased calcium uptake through voltage-gated calcium channels in juvenile and adult-onset iPSCs-based HD models [61]. It is well-known that the length of the huntingtin’s polyglutamine tract directly correlates with the severity of HD and inversely correlates with the age of manifestation of the
disease. At the moment, it has been noted that the amplitude of the store-operated calcium currents and, likely, calcium entry through VGCC did not depend on the length of the polyglutamine tract in the mutant huntingtin [61]. Nevertheless, it was noted that the length of the polyglutamine tract in the mutant huntingtin may impact mitochondrial dysfunction, the severity of DNA damage, and cell death, which was demonstrated on isogenic NPC models of HD (81Q, 65Q, and 45Q) [44]. The most severe alterations were observed for NPC expressed huntingtin with a long polyglutamine tract (81Q).

### Table 3. Alterations in calcium signaling in iPSCs-based models of Huntington’s disease.

| Mutant genes | Cell type | Disturbance associated with calcium signaling |
|--------------|-----------|---------------------------------------------|
| iPSCs        | GABAergic neurons | Increased store-operated calcium entry and calcium currents through voltage-gated calcium channels in low-repet and juvenile models of Huntington’s disease [8,61,157] |
| NPC          | GABAergic neurons | Increased mitochondrial density [156] |
| NPC          | GABAergic neurons | Dysfunction of lysosomes and autophagy [8,155] |
| NPC          | Isogenic models   | Mitochondrial dysfunction, bioenergetic defects [44,161] |

HD is also characterized by mitochondria dysfunction: decreased mitochondrial density [156], the level of adenosine triphosphate (ATP), and decreased expression of glycolytic enzymes [161]. ATP levels in the neurons of HD patients can be restored by the addition of pyruvate; thus, pyruvate or other related metabolic supplements may have a therapeutic effect in HD [161]. A promising modulator of calcium signaling that can be used in the treatment of HD is EVP4593 compound. It has been shown that EVP4593 has neuroprotective properties [5,162], including in iPSCs-based models [8]. EVP4593 restored pathologically enhanced store-operated calcium entry [8,157], as well as reduced the level of huntingtin and the STIM2 with prolonged incubation (24 h) [61]. Also, the increased formation of lysosomes and autophagosomes have been reported in HD iPSCs-based models [8,155]. In turn, the compound EVP4593 normalized the number of lysosomes/autophagosomes in iPSCs-based HD neurons [8]. In HD-specific astrocytes, impaired calcium signaling (lengthening of spontaneous calcium oscillations) was noted [166], and impaired transepithelial was shown in endothelial cells [71]. Thus, using HD iPSCs-based models, it was possible to get closer to understanding the mechanisms of aberrant calcium signaling from the impaired
expression of genes responsible for calcium signaling to the dysfunction of ion channels and mitochondria.

8. Spinocerebellar Ataxias

Spinocerebellar ataxias (SCAs) are a large (over 40 disorders) and diverse group of inherited neurodegenerative pathologies [163]. All of them are characterized by the progressive degeneration of the cerebellum, especially Purkinje cells [164]. Great success in obtaining a Purkinje cell culture differentiated from mouse [165,166] and human ESCs [47], and subsequently from iPSCs obtained from healthy donors and patients with SCA 42 [167] and SCA 6 [140], was achieved by the Japanese group of Yoshiki Sasai and Keiko Muguruma. These works showed that Purkinje cells can be obtained in 3D culture, which reproduces the microenvironment in vivo well [42,47,165,166,168,169]. However, the creation of iPSCs-based SCA models based on Purkinje cells remains a complicated task. Currently, only a few protocols for the differentiation of iPSCs into Purkinje cells are known [42,170–173]. There are few other iPSCs-based models of SCA; thus, obtaining further models remains an important task. The first iPSCs-based SCA model was investigated in 2011 [58]. Currently, the presented iPSCs-based SCA models are (Table 4): SCA 1 [174,175], SCA 2 [176–178], SCA 3 [58–60,178–188], SCA 6 [42,189], SCA 7 [190–192], SCA 14 [193], SCA 16 [194], SCA 36 [195], and SCA 42 [167]. More data accumulated on iPSCs-based models of different SCAs can be found in the review by Hommersom et al., 2021 [196].

It is known that SCA types 6 and 42 arise as a result of mutations in the CACNA1A and CACNA1G genes encoding voltage-gated P/Q- and T-type calcium channels, respectively [197]. Depending on the results of alternative splicing, the CACNA1A gene can encode not only the α1A subunit of the voltage-gated P/Q calcium channel, but also the α1ACT transcription factor. Ishida’s group focused on the dysregulation of α1ACT-dependent gene expression and the vulnerability of cells to oxidative stress [42]. In the work of Bavassano’s group, the authors investigated the expression and function of the CACNA1A gene products in a 2D culture of iPSCs-based neurons obtained from patients with SCA 6. Expression levels of CACNA1A encoding the α1A subunit were similar between SCA6 and control neurons, and no differences were found in the subcellular distribution of the Cav2.1 channel. Electrophysiological data showed that the obtained voltage-dependent calcium currents were sensitive to the selective blocker of P/Q channels ω-agatoxin IVA; however, no differences in the amplitudes of currents were found between normal and pathological conditions. The authors suggested that the absence of differences was due to use of the model, as the disease has a late age of manifestation, and the neurons obtained in culture were not mature enough to reveal the pathological phenotype [189]. Moreover, it can be suggested that the absence of differences is due to the use of GABA and glutamatergic neurons but not a Purkinje cell, which is well-known to be a primary target in ataxias.

The role of the p.Arg1715His mutation in the CACNA1G gene on neurogenesis has also been studied [167]. In that work, Purkinje cells differentiated from iPSCs of healthy donors and patients with SCA 42 did not demonstrate significant differences in either the morphology of the dendritic tree or the expression of markers of Purkinje cells (L7 and GRID2, a specific glutamate receptor of Purkinje cells); therefore, this mutation likely does not affect cell differentiation [167]. Unfortunately, there are currently no data on the effect of the p.Arg1715His mutation in the CACNA1G gene on the functioning of voltage-gated T-type calcium channels (Cav3.1) obtained from iPSCs-based models. However, it is known that this mutation affects the voltage sensor (segment S4) Cav3.1 and leads to a shift in the activation curve of mutant channels toward positive potentials compared to the control, without changing the maximum amplitude of currents through Cav3.1 [167].
Table 4. Alterations in calcium signaling in iPSCs-based models of spinocerebellar ataxias.

| Spinocerebellar Ataxias | iPSCs-based models |
|-------------------------|--------------------|
| The most vulnerable areas of the brain | |
| iPSCs | [193] |
| NPC | [176,177] |
| Neurons | [58–60,174,175,180,182–188,190,192] |
| Cortical neurons | [179,181,194] |
| Motoneurons (MNs) | [195] |
| GABAergic and glutamatergic neurons | [189] |
| Purkinje cells | [167,170–173] |
| Mixed cultures | [178] |
| Isogenic models | |
| NPC | [191] |
| Purkinje cells | [42] |

| Mutant genes | Cell type | Disturbance associated with calcium signaling |
|--------------|-----------|--------------------------------------------|
| ATXN1 (SCA1) | GABAergic neurons | Decreased store-operated calcium entry, no changes in the functioning of voltage-gated calcium channels. Vigont et al., unpublished data |
| ATXN2 & 3 (SCA2 & 3) | Mixed cultures | Altered expression of glutamate receptor subunits and other participants in calcium signaling. Increased calcium concentration in the cytosol. Distorted mitochondrial microstructures and mitochondrial dysfunction. [178] |
| ATXN3 (SCA3) | Cortical neurons | Mitochondrial fragmentation and cristae alterations leading to decreased capacity of mitochondrial respiration, impaired mitochondrial degradation. Enhanced calpains-activated ataxin 3 cleavage and produce ataxin 3 fragments. [58,179,181] |
| CACNA1A (SCA6) | GABAergic & glutamatergic neurons | No differences in both CACNA1A expression and amplitudes of voltage-gated calcium currents. [189] |
| ATXN7 (SCA7) | NPC | Decreased mitochondrial network length. Mitochondrial dysfunction, reduced oxygen consumption rate and increased extracellular acidification rate. [191] |
| TBP (SCA17) | GABAergic neurons | Increased store-operated calcium entry and voltage-gated calcium uptake. Vigont et al., unpublished data |

Currently, interesting data demonstrating aberrant calcium signaling have been obtained in iPSCs-based models of polyglutamine ataxias, including SCA1, SCA2, SCA3, SCA7, and SCA17. According to our unpublished data, SCA1 and SCA17 are characterized by the disturbance of calcium signaling. We have shown an increase in store-operated calcium entry and calcium entry through VGCC in SCA17 GABAergic MSNs, which are also highly vulnerable in SCA17 as well as in HD (Vigont et al., unpublished data). In contrast, we observed a decrease in the store-operated calcium entry in SCA1 and no changes in the functioning of voltage-gated calcium channels in GABAergic neurons, which are not affected in SCA1 (Vigont et al., unpublished data). Unfortunately, at present, there is a lack of iPSCs-based models of SCA1 and SCA17, except for studies on differentiated neurons...
from patients with SCA1 [174,175] and the characterization of iPSCs from patients with SCA17 [198].

For SCA2 and SCA3, a change in the expression of the gene encoding subunits of glutamate receptors and other proteins involved in calcium signaling was shown. Significant suppression of gene expression and a decrease in the amount of glutamate receptor protein (GRIA4) and other participants in calcium signaling was noted in SCA3 when cells were incubated in a medium with glutamate [178]. In the presence of glutamate, neuronal death has also been increased; especially in SCA3, an increase in the concentration of cytosolic calcium occurs, and mitochondrial dysfunction is observed [178]. The use of glutamate receptor blockers prevented the release of calcium into the cytosol, leading to a mitigation of the pathological phenotype in SCA2 and SCA3. The most effective drug for arresting the pathological effects in SCA3 was dantrolene, which is known as a ryanodine receptor antagonist. This agent reduced cell death and the amount of calcium in the cytosol, as well as restored mitochondrial function [178]. Riluzole has been shown to be effective in the treatment of both SCA2 and SCA3. The less effective substances were MK801 and NBQX, known as NMDAR and AMPAR antagonists, respectively [178].

The production and accumulation of mutant polyglutamine proteins lead to the formation of intracellular aggregates. It was found that the formation of aggregates of mutant ataxin 3 is a calcium-dependent process. Treatment of iPSCs-based SCA3 neurons with glutamate enhanced the cleavage of ataxin 3, which was accompanied by the accumulation of its fragments and the formation of aggregates, leading to a decrease in the lifespan of neurons. In turn, blockers of calpain, which require calcium for its activation, had a neuroprotective effect and prevented the formation of aggregates [58]. Calpain-induced cleavage of ataxin 3 led to the formation of ataxin 3 fragments causing mitochondria fragmentation and cristae damage as well as disrupting the respiratory function of mitochondria, in addition to mitochondria degradation [179,181]. Notably, these alterations were not observed in both SCA3 fibroblasts [58] and NPS [188] but only in mature neurons.

Spinocerebellar ataxia type 7 (SCA7) is another polyglutamine disorder characterized by degeneration of the cerebellum and retina. Patients with SCA7 demonstrated atrophy of the cerebellar cortex and brainstem and significant loss of Purkinje cells. An important feature of SCA7 that distinguishes it from other spinocerebellar ataxias is retinal degeneration. As the disease progresses, dysfunction turns into complete blindness. Many clinical features of SCA7 were observed in mitochondrial diseases; therefore, it is interesting to study the functioning of mitochondria in patients with SCA7. NPCs obtained from iPSCs from patients with SCA7 showed a decrease in the length of the mitochondrial network. The strong changes were observed in a SCA7 patient with 70 glutamine residues in polyQ tract in ataxin7 (70Q) but only minor changes were detected in patients with a shorter mutant polyQ tract (50Q) and (65Q). It has been shown that the length of the mitochondrial network is reduced depending on the length of the polyglutamine tract in isogenic cell lines. In addition, NPCs producing ataxin7-113Q showed a marked decrease in the oxygen consumption rate (OCR) and a significant increase in the extracellular acidification rate (ECAR), which was possibly caused by a significant decrease in the NAD$^+$ level in SCA7 NPC [191].

9. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is one of the most severe neurodegenerative pathologies with the predominant death of motoneurons (MNs). Therefore, differentiated patient-specific motor neurons [64,199–219], as well as isogenic models [220–223], have been widely used to model this pathology since 2008. It is important to note that in the published papers, the proportion of MNs from the differentiated cells varies from 30% to 95% (Table 5). In Table 5, all the presented models are marked as “motoneurons.” Optimization of the protocols of iPSCs differentiation into MNs remains an important task. In addition to MNs, cortical neurons [205], astrocytes [202,224,225], and oligodendrocytes [226] were presented. More than 90% of cases of ALS are sporadic. Hereditary forms of ALS are associated mainly
with mutations in the genes: SOD1 (superoxide dismutase 1) [227], TDP-43 or TARDBP ( TAR DNA binding protein) [228], C9orf72 (chromosome 9 open reading frame 72) [229], and FUS (fused in sarcoma) [230]. Due to the use of iPSCs-based models, not only are hereditary forms of ALS currently being studied, but so are sporadic cases of ALS [205,209,215,216]. In iPSCs-based models of hereditary and sporadic ALS, changes in both gene expression and functional alterations associated with the mitochondria and calcium signaling were noted.

Table 5. Alterations in calcium signaling in iPSCs-based models of amyotrophic lateral sclerosis.

| Mutant genes | Cell type | Disturbance associated with calcium signaling |
|--------------|-----------|---------------------------------------------|
| C9orf72      | MNs       | Transcriptional changes in levels of the mitochondrial transporter, increased expression of genes encoding glutamate receptors and VGCC. Increased glutamate excitotoxicity C9orf72 iPSCN cultures. Disrupted mitochondrial calcium buffering capacity, low calbindin levels. [204,217–219,221] |
| TARDBP       | MNs       | Increased expression of genes encoding glutamate receptors. Elevated basal intracellular calcium levels. Increased conductance for calcium AMPA and NMDA receptors. Imbalance in mitochondrial calcium buffering capacity. [217–219] |
| SOD1         | MNs       | Transcriptional and functional changes: defects in mitochondrial transport, morphology and motility, increase in mitochondrial density; oxidative and ER-related stress. Reduced level of calcium-binding proteins. [220,221] |
| FUS          | MNs       | No morphological changes in the mitochondria, decreased mitochondrial motility. [223] |
| Sporadic form | MNs      | Deregulated expression of the genes associated with mitochondrial functioning. [209] |

In iPSCs-based MNs with a mutation in the C9orf72 gene, an increase in the calcium influx to the cytosol after depolarization and a slow recovery up to physiological conditions was shown [219]. This study also demonstrated a decrease in the amount of calbindin, which may reduce calcium buffering capacity in the cytosol. [219]. C9orf72 ALS MNs were found to be more sensitive to glutamate treatment than control cells [204]. At the same time, glutamate-induced cell death was compensated for by treatment with blockers of glutamate receptors and calcium channels (MK-801, 10 µM; CNQX, 10 µM; nimodipine, 2 µM) [204]. Motor neurons with the TARDBP mutation showed high basal levels of intracellular calcium [218], as well as increased glutamate-induced calcium entry into the cytosol. Both MNs with mutations in C9orf72 and TARDBP have been shown to have a greater conductance of AMPA and NMDA receptors for calcium [219]. In addition, an increase in the expression of genes encoding kainate, AMPA, and NMDA receptors [217], as well as VGCC subunits [218], have been reported. No differences were found in the expression of genes encoding the Orai1, STIM1, and SERCA1 proteins involved in the store-
operated calcium entry [218]. At the same time, a decrease in the thapsigargin-induced release of calcium from the ER with mutations in the SOD1, FUS, and TDP43 genes was noted [218]. Motor neurons with a mutation in SOD1 were characterized by changes in gene expression and functional disorders associated with the mitochondria. There was a change in morphology, a decrease in mobility, and an increase in the density of mitochondria [224]. Some mitochondrial disorders are also characteristic of MNs with mutations in C9ORF72 and TARDBP: a decrease in the mitochondrial membrane potential [212], a decrease in the calcium buffering capacity [219], and dysfunction of mitochondrial uniporters [219,221].

MNs with the FUS mutation are characterized by the absence of morphological changes in mitochondria; however, a decrease in their motility was noted. Moreover, the severity of the impairment increases with the maturation of neurons [223]. For sporadic cases of ALS, changes in gene expression associated with mitochondrial function were noted [209]. Motor neurons with a mutation in SOD1 were also characterized by oxidative and ER stress, hyperexcitability of neurons [221], and a decreased level of calcium-binding proteins CDH23 and CALU [220].

The data analysis allows us to conclude that the aberrant calcium signaling observed in ALS highly varies depending on the gene in which the mutation occurs [219,221] (Table 5).

10. Other Neurological Diseases

10.1. Autism Spectrum Disorders

Autism spectrum disorders (ASD) are a heterogeneous group of pathologies associated with impairments in the development of the nervous system. ASD have an unclear etiology: A fairly large number of gene mutations that can be associated with autism has been identified. Among them are the genes responsible for the functioning of voltage-gated calcium channels (VGCC): CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1E, CACNA1F, CACNA1G, CACNA1H, and CACNA1I as well as accessory subunits CACNB2, CACNA2D3, and CACNA2D4 [231].

Timothy’s syndrome is a prominent example of ASD associated with mutations in voltage-gated channels. This pathology results from a mutation in the CACNA1C gene encoding voltage-gated L-type calcium channels (Cav1.2) [232]. The mutation is localized in the S6 segment and leads to impaired inactivation of the Cav1.2 channels [232]. ASD are characterized mostly by the dysfunction of cortical neurons; therefore, ASD including Timothy’s syndrome are commonly modeled by iPSCs-based cortical neurons. Recent data on modeling Timothy’s syndrome on patient-specific neurons are presented in detail in a review [233]. iPSCs-based neurons from patients with Timothy’s syndrome were characterized by a decrease in the dendritic tree [234]. Using calcium imaging (Fura 2AM), a significant increase in the depolarization-induced calcium influx, which was sensitive to the L-type calcium channel blocker nimodipine, has been shown in iPSCs-based neurons of patients with Timothy’s syndrome (Table 6). Also, using Illumina microarrays, changes in the expression of 223 genes in patients with Timothy’s syndrome were shown, some of which are responsible for calcium signaling [235]. In addition, it has been shown that VGCC in Timothy’s syndrome are involved in neuronal differentiation and developmental regulation [236].

It is also important to note that disturbances in the functioning of voltage-gated calcium channels can be caused not only by mutations of the genes encoding them but also by the dysfunction of regulatory proteins. For example, neurexins are transmembrane, predominantly presynaptic proteins involved in the regulation of different calcium channels, including VGCC. It has been shown that neurons with a mutation in the neurexin gene (NRXN1α +/-) obtained from iPSCs of patients with autism exhibit changed VGCC functioning with an increased frequency, duration, and amplitude of calcium oscillations [238].
Table 6. Alterations in calcium signaling in iPSCs-based models of other neurological diseases.

| Other Neurological Pathologies                  | iPSCs-based models |
|------------------------------------------------|--------------------|
| The most vulnerable areas of the brain         | Patient-specific models |
| NPC (LS)                                       | [237]              |
| Neurons (ASD)                                 | [234–236]          |
| Cortical neurons (ASD)                         | [238]              |
| Mutant genes                                   | Cell type           |
| Genes encoding VGCC subunits (ASD)             | Neurons             |
| Altered expression of genes responsible for calcium signaling. Dysfunction of voltage-gated channels. Increased nimodipine sensitive calcium influx after depolarization. | [234,235]          |
| mtDNA m.13513G (LS)                            | NPC                |
| Mitochondrial dysfunction, decreased calcium buffering capacity | [237]              |

10.2. Leigh’s Syndrome

Leigh’s syndrome (LS) is the most frequent mitochondrial disorder in infants and is characterized by neurodegeneration and astrogliosis in the basal ganglia or brainstem. There are currently no drugs or effective treatments for this disease, in part due to a lack of relevant models. More recently, an iPSCs-based model of LS carrying the mtDNA m.13513G mutation has been created (Table 6). Characterization of mitochondria, electrophysiological analysis, and calcium imaging in iPSCs-based neurons were carried out. Impairment of oxidative phosphorylation in the neurons of LS patients was clearly demonstrated. This is the first report of electrophysiological studies performed on iPSCs-derived neurons carrying the mtDNA mutation, which showed that affected neurons exhibit mitochondrial dysfunction along with decreased calcium buffering capacity. This can lead to an increase in cytoplasmic calcium concentration and subsequent cell death seen in patients [237].

11. Conclusions

In summation, we can say that iPSCs-based models became important instruments for studying the mechanisms underlying neurodegenerative pathologies and screening potential neuroprotective drugs. In particular, rare pathologies such as HD, SCAs, LS, and others have become available for research. Moreover, iPSCs-based models opened up the possibility of studying sporadic forms of neurodegenerative diseases, which are most common in AD, PD, and ALS. In general, studies carried out using iPSCs-based models reproduce previously obtained data in animal and cellular models, but at the same time significantly deepen our understanding of the molecular mechanisms of pathogenesis. Although the molecular mechanisms of the pathogenesis of various neurodegenerative diseases may differ, aberrant calcium signaling is characteristic of most of them. The most common abnormally fluctuations in calcium signaling in neurodegenerative pathologies include altered functioning of calcium-permeable channels, changes in levels of calcium-binding proteins, and mitochondrial dysfunctions. A stable increase in the concentration of calcium in the cytosol may lead to the launch of the apoptotic cascade and cell death. To prevent cell death, various compensatory mechanisms regulate the dynamics of calcium in the cell. For example, excess calcium can be accumulated in intracellular calcium stores (mitochondria and endoplasmic reticulum) or buffered by calcium-binding proteins. Thus, the often observed alterations in the expression of the genes encoding calcium-binding proteins may be separated from disease causes but represent a compensatory mechanism seeking to prevent cell death.

The collected data allow us to suggest a central role of calcium signaling disturbances in neurodegenerative processes and establish the components of calcium signaling machinery to be a promising target for medical treatment. Summarizing the data, we can also
suggest that the pathological increase of calcium uptake along with the greater calcium release from intracellular stores is more dangerous for cells than pathological attenuation of calcium signaling pathways. So, screening for new drugs in general should focus on finding the novel inhibitors of calcium channels and transporters. Additionally, iPSCs-based models open up studies of the neuronal specificity of the pathological processes and may shed light on the problem of the selective vulnerability of neurons in distinct pathologies. We would like to believe that in the near future the use of iPSCs-based technologies will not only clarify the molecular mechanisms of neurodegenerative processes but also contribute to the development of novel and very specific neuroprotective drugs.

**Author Contributions:** D.A.G.: writing—original draft preparation, writing—review and editing, visualization, conceptualization; E.V.K.: writing—original draft preparation, writing—review and editing, conceptualization, visualization, supervision; V.A.V.: writing—review and editing, conceptualization, supervision, project administration. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Grant from the Ministry of Science and Higher Education of Russia—Research Project N 075-15-2020-795, local identifier 13.1902.21.0027 (DAG, VAV, EVK).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. World Health Organization. Dementia Factsheet. Available online: https://www.who.int/en/news-room/fact-sheets/detail/dementia (accessed on 1 December 2021).
2. Ciobanu, A.M.; Ionita, I.; Buleandra, M.; David, I.G.; Popa, D.E.; Ciucu, A.A.; Budisteauanu, M. Current advances in metabolomic studies on non-motor psychiatric manifestations of Parkinson’s disease (Review). Exp. Ther. Med. 2021, 22, 1010. [CrossRef]
3. Takahashi, K.; Yamanaka, S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Cell 2006, 126, 663–676. [CrossRef]
4. Khachaturian, Z.S. Towards theories of brain aging. In Handbook of Studies on Psychiatry and Old Age; Kay, D.S., Burrows, G.W., Eds.; Elsevier: Amsterdam, The Netherlands, 1984; pp. 7–30.
5. Wu, J.; Shih, H.P.; Vigont, V.; Hrdlicka, L.; Diggins, L.; Singh, C.; Mahoney, M.; Chesworth, R.; Shapiro, G.; Zimina, O.; et al. Neuronal store-operated calcium entry pathway as a novel therapeutic target for Huntington’s disease treatment. Chem. Biol. 2011, 18, 777–793. [CrossRef] [PubMed]
6. Egorova, P.; Popugaeva, E.; Bezprozvanny, I. Disturbed calcium signaling in spinocerebellar ataxias and Alzheimer’s disease. Semin. Cell Dev. Biol. 2015, 40, 127–133. [CrossRef] [PubMed]
7. Huang, D.S.; Lin, H.Y.; Lee-Chen, G.J.; Hsieh-Li, H.M.; Wu, C.H.; Lin, J.Y. Treatment with a Ginkgo biloba extract, EGB 761, inhibits excitotoxicity in an animal model of spinocerebellar ataxia type 17. Drug. Des. Dev. Ther. 2016, 10, 723–731. [CrossRef]
8. Nekrasov, E.D.; Vigont, V.A.; Klyushnikov, S.A.; Lebedeva, O.S.; Vassina, E.M.; Bogomazova, A.N.; Chestkov, I.V.; Semashko, T.A.; Kiseleva, E.; Suldina, L.A.; et al. Manifestation of Huntington’s disease pathology in human induced pluripotent stem cell-derived neurons. Mol. Neurodegener. 2016, 11, 27. [CrossRef] [PubMed]
9. Czeredys, M.; Vigont, V.A.; Boeva, V.A.; Mikoshiba, K.; Kaznacheyeva, E.V.; Kuznicki, J. Huntingtonin-Associated Protein 1A Regulates Store-Operated Calcium Entry in Medium Spiny Neurons from Transgenic YAC128 Mice, a Model of Huntington’s Disease. Front. Cell Neurosci. 2018, 12, 381. [CrossRef] [PubMed]
10. Hisatsune, C.; Hamada, K.; Mikoshiba, K. Ca2+ signaling and spinocerebellar ataxia. Biochim. Biophys. Acta Mol. Cell Res. 2018, 1865 Pt B, 1733–1744. [CrossRef]
11. Evans, M.J.; Kaufman, M.H. Establishment in culture of pluripotent cells from mouse embryos. Nature 1981, 292, 154–156. [CrossRef]
12. Thomson, J.A.; Itskovitz-Eldor, J.; Shapiro, S.S.; Waknitz, M.A.; Swiergiel, J.J.; Marshall, V.S.; Jones, J.M. Embryonic stem cell lines derived from human blastocysts. Science 1998, 282, 1145–1147. [CrossRef]
13. Freude, K.K.; Penjwini, M.; Davis, J.L.; LaFerla, F.M.; Burton-Jones, M. Soluble amyloid precursor protein induces rapid neural differentiation of human embryonic stem cells. J. Biol. Chem. 2011, 286, 24264–24274. [CrossRef]
14. Mertens, J.; Stüber, K.; Poppe, D.; Doerj, J.; Ladewig, J.; Brütsch, O.; Koch, P. Embryonic stem cell-based modeling of tau pathology in human neurons. Am. J. Pathol. 2013, 182, 1769–1779. [CrossRef]
15. Yue, W.; Li, Y.; Zhang, T.; Jiang, M.; Qian, Y.; Zhang, M.; Sheng, N.; Feng, S.; Tang, K.; Yu, X.; et al. ESC-Derived Basal Forebrain Cholinergic Neurons Ameliorate the Cognitive Symptoms Associated with Alzheimer’s Disease in Mouse Models. Stem Cell Rep. 2015, 5, 776–790. [CrossRef] [PubMed]

16. Zeng, X.; Chen, J.; Deng, X.; Liu, Y.; Rao, M.S.; Cadet, J.L.; Freed, W.J. An In Vitro model of human dopaminergic neurons derived from embryonic stem cells: MPP+ toxicity and GDNF neuroprotection. Neuropsychopharmacology 2006, 31, 2708–2715. [CrossRef]

17. Schneider, B.L.; Sehus, C.R.; Capowski, E.E.; Aeabischer, P.; Zhang, S.C.; Svendsen, C.N. Over-expression of alpha-synuclein in human neural progenitors leads to changes in fate and differentiation. Hum. Mol. Genet. 2007, 16, 651–666. [CrossRef]

18. Kriks, S.; Shim, J.W.; Piao, J.; Ganat, Y.M.; Wakeman, D.R.; Xie, Z.; Carrillo-Reid, L.; Auyeung, G.; Antonacci, C.; Buch, A.; et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson’s disease. Nature 2011, 480, 547–551. [CrossRef]

19. Aubry, L.; Bugi, A.; Lefort, N.; Rousseau, F.; Peschanski, M.; Perrier, A.L. Striatal progenitors derived from human ES cells mature into DARPP32 neurons In Vitro and in quinolinic acid-lesioned rats. Proc. Natl. Acad. Sci. USA 2008, 105, 16707–16712. [CrossRef]

20. Niclis, J.; Trounson, A.O.; Dottori, M.; Ellisdon, A.; Bottomley, S.P.; Verlinsky, Y.; Cram, D. Human embryonic stem cell models of Huntington disease. Reprod. Biomed. Online 2009, 19, 106–113. [CrossRef]

21. Moore, L.R.; Keller, L.; Bushart, D.D.; Delatorre, R.G.; Li, D.; McLoughlin, H.S.; do Carmo Costa, M.; Shakkottai, V.G.; Smith, G.D.; Paulson, H.L. Antisense oligonucleotide therapy rescues aggresome formation in a novel spinocerebellar ataxia type 3 human embryonic stem cell line. Stem Cell Rep. 2013, 39, 101504. [CrossRef]

22. Di Giorgio, F.P.; Carrasco, M.A.; Siao, M.C.; Maniatis, T.; Eggan, K. Non-cell autonomous effect of glia on motor neurons in an embryonic stem cell-based ALS model. Nat. Neurosci. 2007, 10, 608–614. [CrossRef]

23. Di Giorgio, F.P.; Boulting, G.L.; Bobrowicz, S.; Eggan, K.C. Human embryonic stem cell-derived motor neurons are sensitive to the toxic effect of glial cells carrying an ALS-causing mutation. Cell Stem Cell 2008, 3, 637–648. [CrossRef]

24. Karumbayaram, S.; Kelly, T.K.; Paucar, A.A.; Roe, A.J.; Umbach, J.A.; Charles, A.; Goldman, S.A.; Kornblum, H.I.; Wiedau-Pazos, M. Human embryonic stem cell-derived motor neurons expressing SOD1 mutants exhibit typical signs of motor neuron degeneration linked to ALS. Dis. Models Mech. 2009, 2, 189–195. [CrossRef]

25. Maroof, A.M.; Keros, S.; Tyson, J.A.; Ying, S.W.; Ganat, Y.M.; Merkle, F.T.; Liu, B.; Goulburn, A.; Stanley, E.G.; Elefanty, A.G.; et al. Directed differentiation and functional maturation of cortical interneurons from human embryonic stem cells. Cell Stem Cell. 2013, 12, 559–572. [CrossRef]

26. Hanna, J.H.; Saha, K.; Jaenisch, R. Pluripotency and cellular reprogramming: Facts, hypotheses, unresolved issues. Cell 2010, 143, 508–525. [CrossRef]

27. Bock, C.; Kiskinis, E.; Verstappen, G.; Gu, H.; Boulting, G.; Smith, Z.D.; Ziller, M.; Croft, G.F.; Amoroso, M.W.; Oakley, D.H.; et al. Reference Maps of human ES and iPS cell variation enable high-throughput characterization of pluripotent cell lines. Cell 2011, 144, 439–452. [CrossRef]

28. Lister, R.; Pelizzola, M.; Kida, Y.S.; Hawkins, R.D.; Nery, J.R.; Hon, G.; Antosiewicz-Bourget, J.; O'Malley, R.; Castanon, R.; Klugman, S.; et al. Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. Nature 2011, 471, 68–73. [CrossRef]

29. Wang, S.N.; Wang, Z.; Xu, T.Y.; Cheng, M.H.; Li, W.L.; Miao, C.Y. Cerebral Organoids Repair Ischemic Stroke Brain Injury. Transl. Stroke Res. 2020, 11, 983–1000. [CrossRef]

30. Wevers, N.R.; Kasi, D.G.; Gray, T.; Wilschut, K.J.; Smith, B.; van Vught, R.; Shimizu, F.; Sano, Y.; Kanda, T.; Marsh, G.; et al. A perfused human blood-brain barrier on-a-chip for high-throughput assessment of barrier function and antibody transport. Fluids Barriers CNS 2018, 15, 23. [CrossRef]

31. Salmon, M.M.; Marsh, G.; Kusters, I.; Delincé, M.; Di Caprio, G.; Upadhyaayula, S.; de Nola, G.; Hunt, R.; Ohashi, K.G.; Gray, T.; et al. Design and Validation of a Human Brain Endothelial Microvessel-on-a-Chip Open Microfluidic Model Enabling Advanced Optical Imaging. Front. Bioeng. Biotechnol. 2020, 8, 573775. [CrossRef]

32. Ellit, M.S.; Barbar, L.; Tesar, P.J. Drug screening for human genetic diseases using iPSC models. Hum Mol Genet 2018, 27, R89–R98. [CrossRef]

33. Aldewachi, H.; Al-Zidan, R.N.; Conner, M.T.; Salman, M.M. High-Throughput Screening Platforms in the Discovery of Novel Drugs for Neurodegenerative Diseases. Bioengineering 2021, 8, 30. [CrossRef]

34. Salmon, M.M.; Al-Obaidi, Z.; Kitchen, P.; Loreto, A.; Bill, R.M.; Wade-Martins, R. Advances in Applying Computer-Aided Drug Design for Neurodegenerative Diseases. Int. J. Mol. Sci. 2021, 22, 4688. [CrossRef]

35. Salmon, M.M.; Kitchen, P.; Yool, A.J.; Bill, R.M. Recent breakthroughs and future directions in drugging aquaporins. Trends Pharmacol. Sci. 2022, 43, 30–42. [CrossRef]

36. An, M.C.; Zhang, N.; Scott, G.; Montoro, D.; Wittkop, T.; Mooney, S.; Melov, S.; Ellerby, L.M. Genetic correction of Huntington’s disease phenotypes in induced pluripotent stem cells. Cell Stem Cell 2012, 11, 253–263. [CrossRef]

37. Israel, M.A.; Yuan, S.H.; Bardy, C.; Reyna, S.M.; Mu, Y.; Herrera, C.; Heffernan, M.P.; Van Gorp, S.; Nazor, K.L.; Boscolo, F.S.; et al. Probing sporadic and familial Alzheimer’s disease using induced pluripotent stem cells. Nature 2012, 482, 216–220. [CrossRef]

38. Woodruff, G.; Young, J.E.; Martinez, F.J.; Buen, F.; Gore, A.; Kinaga, J.; Li, Z.; Yuan, S.H.; Zhang, K.; Goldstein, L.S. The presenilin-1 ΔE9 mutation results in reduced γ-secretase activity, but not total loss of PS1 function, in isogenic human stem cells. Cell Rep. 2013, 5, 974–985. [CrossRef]
39. Fong, H.; Wang, C.; Knoferle, J.; Walker, D.; Balestra, M.E.; Tong, L.M.; Leung, L.; Ring, K.L.; Seeley, W.W.; Karydas, A.; et al. Genetic correction of tauopathy phenotypes in neurons derived from human induced pluripotent stem cells. *Stem Cell Rep*. 2013, 1, 226–234. [CrossRef]

40. Lu, B.; Palacino, J. A novel human embryonic stem cell-derived Huntington’s disease neuronal model exhibits mutant huntingtin (mHTT) aggregates and soluble mHTT-dependent neurodegeneration. *FASEB J*. 2013, 27, 1820–1829. [CrossRef]

41. Shaltouki, A.; Sivapatham, R.; Pei, Y.; Gerencser, A.A.; Momčilović, O.; Rao, M.S.; Zeng, X. Mitochondrial alterations by PARKIN in dopaminergic neurons using PARK2 patient-specific and PARK2 knockout isogenic iPSC lines. *Stem Cell Rep*. 2015, 4, 847–859. [CrossRef]

42. Ishida, Y.; Kawakami, H.; Kitajima, H.; Nishiyama, A.; Sasai, Y.; Inoue, H.; Muguruma, K. Vulnerability of Purkinje Cells Generated from Spino-cerebellar Ataxia Type 6 Patient-Derived iPSCs. *Cell Rep.* 2016, 17, 1482–1490. [CrossRef]

43. Heman-Ackah, S.M.; Manzano, R.; Hoozemans, J.J.M.; Scheper, W.; Flynn, R.; Haerty, W.; Cowley, S.A.; Bassett, A.R.; Wood, M.J.A. Alpha-synuclein induces the unfolded protein response in Parkinson’s disease SNCA triplication iPSC-derived neurons. *Hum. Mol. Genet.* 2017, 26, 4441–4450. [CrossRef]

44. Ooi, J.; Langley, S.R.; Xu, X.; Utami, K.H.; Sim, B.; Huang, Y.; Harmston, N.P.; Tay, Y.L.; Ziaei, A.; Zeng, R.; et al. Unbiased profiling of isogenic Huntington disease hPSC-derived CNS and peripheral cells reveals strong cell-type specificity of CAG length effects. *Cell Rep.* 2019, 123, 48–57. [CrossRef]

45. Tagliaferro, L.; Zamora, M.E.; Chiba-Falek, O. Multiplication of the SNCA locus exacerbates neuronal nuclear aging. *Hum. Mol. Genet.* 2019, 28, 407–421. [CrossRef]

46. Choi, S.H.; Kim, Y.H.; Hebisch, M.; Sliwinski, C.; Lee, S.; D’Avanzo, C.; Chen, H.; Hooli, B.; Asselin, C.; Muffat, J.; et al. A three-dimensional human neuronal cell model of Alzheimer’s disease. *Nature* 2014, 515, 274–278. [CrossRef]

47. Munegu, M.; Ishii, Y.; Kawakami, H.; Hashimoto, K.; Sasai, Y. Self-Organization of Polarized Cerebellar Tissue in 3D Culture of Human Pluripotent Stem Cells. *Cell. Rep.* 2015, 10, 537–550. [CrossRef]

48. Raja, W.K.; Mungenast, A.E.; Lin, Y.T.; Ko, T.; Abdurrob, F.; Seo, J.; Tsai, L.H. Self-Organizing 3D Human Neural Tissue Derived from Induced Pluripotent Stem Cells Recapitulate Alzheimer’s Disease Phenotypes. *PloS ONE* 2016, 11, e0161969. [CrossRef]

49. Conforti, P.; Besussu, D.; Bocchi, V.D.; Faedo, A.; Cesana, E.; Rossetti, G.; Ranzani, S.; Svendsen, C.N.; Thompson, L.M.; Toselli, M.; et al. Faulty neuronal determination and cell polarization are reverted by modulating HD early phenotypes. *Proc. Natl. Acad. Sci. USA* 2018, 115, E762–E771. [CrossRef]

50. Świtonska, K.; Szlachcic, W.J.; Handschuh, L.; Wojciechowski, P.; Marczak, L.; Stelmaszczyk, M.; Figlerowicz, M.; Figiel, M. Identification of altered developmental pathways in human juvenile HD iPSC and 71Q and 109Q using transcriptome profiling. *Front Cell Neurosci.* 2018, 12, 528. [CrossRef]

51. Imaizumi, Y.; Okada, Y.; Akamatsu, W.; Koike, M.; Kuzumaki, N.; Hayakawa, H.; Nihira, T.; Kobayashi, T.; Ohyama, M.; Sato, S.; et al. Mitochondrial dysfunction associated with increased oxidative stress and α-synuclein accumulation in PARK2 iPSC-derived neurons and postmortem brain tissue. *Mol. Brain* 2012, 5, 35. [CrossRef]

52. Ring, K.L.; An, M.C.; Zhang, N.; O’Brien, R.N.; Ramos, E.M.; Gao, F.; Atwood, R.; Bailus, B.J.; Melov, S.; Mooney, S.D.; et al. Genomic Analysis Reveals Disruption of Striatal Neuronal Development and Therapeutic Targets in Human Huntington’s Disease Neuronal Stem Cells. *Stem Cell Rep.* 2015, 5, 1023–1038. [CrossRef]

53. Vierbuchen, T.; Ostermeier, A.; Pang, Z.P.; Kokubu, Y.; Südhof, T.C.; Wernig, M. Direct conversion of fibroblasts to functional neurons by definedfactors. *Nature* 2010, 463, 1035–1041. [CrossRef] [PubMed]

54. Ambasudhan, R.; Talavantora, M.; Coleman, R.; Yuan, X.; He, W.; Song, B.; Xian, Y.; Fan, D.; OuYang, S.; et al. Autophagy Promoted the Degradation of Mutant ATXN3 in Neurologically Differentiated Spino-cerebellar Ataxia-3 Human Induced Pluripotent Stem Cells. *Biomed. Res. Int.* 2016, 6701793. [CrossRef]

55. Yoo, A.S.; Sun, A.X.; Li, L.; Scheglovitov, A.; Portmann, T.; Li, Y.; Lee-Messer, C.; Dolmetsch, R.E.; Tsien, R.W.; Crabtree, G.R. MicroRNA-mediated conversion of human fibroblasts to neurons. *Nature* 2011, 476, 228–231. [CrossRef] [PubMed]

56. Victor, M.B.; Richner, M.; Hermanstyne, T.O.; Ransell, J.L.; Sobieski, C.; Deng, P.Y.; Klyachko, V.A.; Nerbonne, J.M.; Yoo, A.S. Generation of human striatal neurons by microRNA-dependent direct conversion of fibroblasts. *Neuron* 2014, 84, 311–323. [CrossRef] [PubMed]

57. Hu, W.; Qiu, B.; Guan, W.; Wang, Q.; Wang, M.; Li, W.; Gao, L.; Shen, L.; Huang, Y.; Xie, G.; et al. Direct conversion of human fibroblasts into functional neurons under defined conditions. *Cell Stem Cell* 2011, 9, 113–118. [CrossRef]

58. Yoo, A.S.; Sun, A.X.; Li, L.; Scheglovitov, A.; Portmann, T.; Li, Y.; Lee-Messer, C.; Dolmetsch, R.E.; Tsien, R.W.; Crabtree, G.R. MicroRNA-mediated conversion of human fibroblasts to neurons. *Nature* 2011, 476, 228–231. [CrossRef] [PubMed]

59. Victor, M.B.; Richner, M.; Hermanstyne, T.O.; Ransell, J.L.; Sobieski, C.; Deng, P.Y.; Klyachko, V.A.; Nerbonne, J.M.; Yoo, A.S. Generation of human striatal neurons by microRNA-dependent direct conversion of fibroblasts. *Neuron* 2014, 84, 311–323. [CrossRef] [PubMed]

60. Ou, Z.; Luo, M.; Niu, X.; Chen, Y.; Xie, Y.; He, W.; Song, B.; Xian, Y.; Fan, D.; OuYang, S.; et al. Autophagy Promoted the Degradation of Mutant ATXN3 in Neurologically Differentiated Spino-cerebellar Ataxia-3 Human Induced Pluripotent Stem Cells. *Biomed. Res. Int.* 2016, 6701793. [CrossRef] [PubMed]

61. Vigont, V.A.; Grekhnev, D.A.; Lebedeva, O.S.; Gusev, K.O.; Volovikov, E.A.; Skopin, A.Y.; Bogomazova, A.N.; Shuvalova, L.D.; Zubkova, O.A.; Khomyakova, E.A.; et al. STIM2 Mediates Excessive Store-Operated Calcium Entry in Patient-Specific
iPSC-Derived Neurons Modeling a Juvenile Form of Huntington’s Disease. Front. Cell Dev. Biol. 2021, 9, 625231. [CrossRef] [PubMed]

62. Chambers, S.M.; Qi, Y.; Mica, Y.; Lee, G.; Zhang, X.J.; Niu, L.; Bilsland, J.; Cao, L.; Stevens, E.; Whiting, P.; et al. Combined small-molecule inhibition accelerates developmental timing and converts human pluripotent stem cells into nociceptors. Nat. Biotechnol. 2012, 30, 715–720. [CrossRef]

63. Shi, Y.; Kirwan, P.; Livesey, F.J. Directed differentiation of human pluripotent stem cells to cerebral cortex neurons and neural networks. Nat. Protoc. 2012, 7, 1836–1846. [CrossRef] [PubMed]

64. Sances, S.; Bruijn, L.I.; Chandran, S.; Eggan, K.; Ho, R.; Klim, J.R.; Livesey, M.R.; Lowry, E.; Macklis, J.D.; Rushton, D.; et al. Modeling ALS with motor neurons derived from human induced pluripotent stem cells. Nat. Neurosci. 2016, 19, 542–553. [CrossRef] [PubMed]

65. Leventou, N.; Morimoto, S.; Imaiizu, K.; Sato, Y.; Takahashi, S.; Mashima, K.; Ishikawa, M.; Sonn, I.; Kondo, T.; Watanabe, H.; et al. Human Astrocytes Model Derived from Induced Pluripotent Stem Cells. Cells 2020, 9, 2680. [CrossRef]

66. Filippini, A.; Mutti, V.; Faustini, G.; Longhena, F.; Ramazzina, I.; Rizzi, F.; Kaganovich, A.; Roosen, D.A.; Landeck, N.; Duffy, M.; et al. Extracellular clusterin limits the uptake of α-synuclein fibrils by murine and human astrocytes. Glia 2021, 69, 681–696. [CrossRef] [PubMed]

67. Abuammar, H.; Bhattacharjee, A.; Simon-Vecsei, Z.; Blasty, K.; Jadiya, P.; Garbincius, J.F.; Elrod, J.W. Reappraisal of metabolic dysfunction in neurodegeneration: Focus on mitochondrial transcription factors. Proc. Natl. Acad. Sci. USA 2017, 114, E2243–E2252. [CrossRef]

68. Lim, R.G.; Quan, C.; Reyes-Ortiz, A.M.; Lutz, S.E.; Kedaigle, A.J.; Gipson, T.A.; Wu, J.; Vatine, G.D.; Stockdale, J.; Casale, M.S.; et al. Huntington’s Disease iPSC-Derived Brain Microvascular Endothelial Cells Reveal WNT-Mediated Angiogenic and Blood-Brain Barrier Deficits. Cell Rep. 2017, 19, 1365–1377. [CrossRef] [PubMed]

69. Katt, M.E.; Mayo, L.N.; Ellis, S.E.; Mahairaki, V.; Rothstein, J.D.; Cheng, L.; Searson, P.C. The role of mutations associated with familial neurodegenerative disorders on blood-brain barrier function in an iPSC model. Fluids Barriers CNS 2019, 16, 20. [CrossRef]

70. HD iPSC Consortium. Developmental alterations in Huntington’s disease neural cells and pharmacological rescue in cells and mice. Nat. Neurosci. 2017, 20, 648–660. [CrossRef]

71. Jadiya, P.; Garbincius, J.F.; Elrod, J.W. Reappraisal of metabolic dysfunction in neurodegeneration: Focus on mitochondrial function and calcium signaling. Acta Neuropathol. Commun. 2021, 9, 124. [CrossRef]

72. Godoy, J.A.; Rios, J.A.; Picón-Págès, P.; Herrera-Fernández, V.; Swaby, B.; Crepin, G.; Vicente, R.; Fernández-Fernández, J.M.; Muñoz, F.J. Mitostasis, Calcium and Free Radicals in Health, Aging and Neurodegeneration. Acta Neuropathol. Commun. 2017, 5, 102130. [CrossRef] [PubMed]

73. HD iPSC Consortium. Developmental alterations in Huntington’s disease neural cells and pharmacological rescue in cells and mice. Nat. Neurosci. 2017, 20, 648–660. [CrossRef]

74. Berridge, M.J. The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. Trends Mol. Med. 2009, 15, 89–100. [CrossRef]

75. Bezprozvanny, I. Calcium signaling and neurodegenerative diseases. Trends Mol. Med. 2009, 15, 89–100. [CrossRef]

76. Berridge, M.J. The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. Physiol. Rev. 2016, 96, 1261–1296. [CrossRef] [PubMed]
87. Secco, A.; Bagetta, G.; Amantea, D. On the Role of Store-Operated Calcium Entry in Acute and Chronic Neurodegenerative Diseases. Front. Mol. Neurosci. 2016, 11, 87. [CrossRef] [PubMed]

88. Wegierski, T.; Kuznicki, J. Neuronal calcium signaling via store-operated channels in health and disease. Cell Calcium 2018, 74, 102–111. [CrossRef] [PubMed]

89. Khachaturian, Z.S. Calcium hypothesis of Alzheimer’s disease and brain aging. Ann. N. Y. Acad. Sci. 1994, 747, 1. [CrossRef]

90. Bezprozvanny, I.; Hayden, M.R. Deranged neuronal calcium signaling and Huntington disease. Biochem. Biophys. Res. Commun. 2004, 322, 1310–1317. [CrossRef]

91. Bezprozvanny, I. Calcium hypothesis of neurodegeneration—An update. Biochem. Biophys. Res. Commun. 2019, 520, 667–669. [CrossRef]

92. Braak, H.; Braak, E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol. 1991, 82, 239–259. [CrossRef]

93. Hoogendijk, W.J.G.; Pool, C.W.; Troost, D.; Van Zwieten, E.; Swaab, D.F. Image analyser-assisted morphometry of the locus coeruleus in Alzheimer’s disease, parkinsonian disease and amyotrophic lateral sclerosis. Brain 1995, 118, 131–143. [CrossRef]

94. Zarow, C.; Lyness, S.A.; Mortimer, J.A.; Chui, H.C. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch. Neurol. 2003, 60, 337–341. [CrossRef]

95. Theofilas, P.; Ehrenberg, A.J.; Dunlop, S.; Di Lorenzo Alho, A.T.; Nguy, A.; Leite, R.E.P.; Rodrigue, R.D.; Mejia, M.B.; Suemoto, C.K.; Ferrerita-Redustini, R.E.L.; et al. Locus coeruleus volume and cell population changes during Alzheimer’s disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. Alzheimer’s Dement. 2017, 13, 236–246. [CrossRef] [PubMed]

96. Montine, T.J.; Phelps, C.H.; Beach, T.G.; Bigio, E.H.; Cairns, N.J.; Dickson, D.W.; Duyckaerts, C.; Frosch, M.P.; Masliah, E.; Mirra, S.S.; et al. National institute on aging-Alzheimer’s association guidelines for the neuropathologic assessment of Alzheimer’s disease: A practical approach. Acta Neuropathol. 2012, 123, 1–11. [CrossRef] [PubMed]

97. Yagi, T.; Ito, D.; Okada, Y.; Akamatsu, W.; Nihei, Y.; Yoshizaki, T.; Yamanaka, S.; Okano, H.; Suzuki, N. Modeling familial Alzheimer’s disease with induced pluripotent stem cells. Hum. Mol. Genet. 2011, 20, 4530–4539. [CrossRef] [PubMed]

98. Ko, H.J.; Choi, S.J.; Wang, Y.H.; Wong, Y.H.; Lai, Y.; Chou, C.H.; Wang, C.; Loh, J.K.; Lieu, A.S.; Cheng, J.T.; et al. GSK3-Mediated Anchoring Increases Phosphorylation of Tau by PKA but Not by GSK3beta via AMP/PKA/GSK3/Tau Axis Signaling in Cerebrospinal Fluid and iPS Cells in Alzheimer Disease. J. Clin. Med. 2019, 8, 1751. [CrossRef]

99. Yin, J.; Van Dongen, A.M. Enhanced Neuronal Activity and Asynchronous Calcium Transients Revealed in a 3D Organoid Model of Alzheimer’s Disease. ACS Biomater. Sci. Eng. 2021, 7, 254–264. [CrossRef]

100. Sproul, A.A.; Jacob, S.; Pre, D.; Kim, S.H.; Nestor, M.W.; Navarro-Sobrino, M.; Santa-Maria, I.; Zimmer, D.; Aubry, S.; Steele, J.W.; et al. Characterization and molecular profiling of PSEN1 familial Alzheimer’s disease iPSC-derived neural progenitors. PLoS ONE 2014, 9, e84547. [CrossRef]

101. Muratore, C.R.; Rice, H.C.; Srikanth, P.; Callahan, D.G.; Shin, T.; Benjamin, L.N.; Walsh, D.M.; Selkoe, D.J.; Young-Pearse, T.L. The familial Alzheimer’s disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons. Hum. Mol. Genet. 2014, 23, 3523–3536. [CrossRef] [PubMed]

102. Kondo, T.; Imamura, K.; Funayama, M.; Tsukita, K.; Miyake, M.; Ohta, A.; Woltjen, K.; Nakagawa, M.; Asada, T.; Arai, T.; et al. iPSC-Based compound screening and In Vitro trials identify a synergistic anti-amyloid beta combination for Alzheimer’s disease. Cell Rep. 2017, 21, 2304–2312. [CrossRef]

103. Birnbaum, J.H.; Wanner, D.; Gietl, A.F.; Saake, A.; Kündig, T.M.; Hock, C.; Nitsch, R.M.; Tackenberg, C. Oxidative stress and altered mitochondrial protein expression in the absence of amyloid-β and tau pathology in iPS-derived neurons from sporadic Alzheimer’s disease patients. Stem Cells 2018, 27, 121–130. [CrossRef]

104. Chen, H.; Cross, A.C.; Thakkar, A.; Xu, H.; Li, A.; Paull, D.; Noggle, S.A.; Kruger, L.; Denton, T.T.; Gibson, G.E. Selective linkage of mitochondrial enzymes to intracellular calcium stores differs between human-induced pluripotent stem cells, neural stem cells, and neurons. J. Neurochem. 2021, 156, 867–879. [CrossRef]

105. Kondo, T.; Asai, M.; Tsukita, K.; Kuto, Y.; Ohsawa, Y.; Sunada, Y.; Imamura, K.; Egawa, N.; Yahata, N.; Okita, K.; et al. Modeling Alzheimer’s disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness. Cell Stem Cell. 2013, 12, 487–496. [CrossRef]

106. Wang, C.; Ward, M.E.; Chen, R.; Liu, K.; Tracy, T.E.; Chen, X.; Xie, M.; Sohn, P.D.; Ludwig, C.; Meyer-Franke, A.; et al. Scalable Production of iPSC-Derived Human Neurons to Identify Tau-Lowering Compounds by High-Content Screening. Stem Cell Rep. 2017, 9, 1221–1233. [CrossRef] [PubMed]

107. Muñoz, S.S.; Engel, M.; Balez, R.; Do-Ha, D.; Cabral-da-Silva, M.C.; Hernández, D.; Berg, T.; Fifixta, J.A.; Grima, N.; Yang, S.; et al. A Simple Differentiation Protocol for Generation of Induced Pluripotent Stem Cell-Derived Basal Forebrain-Like Cholinergic Neurons for Alzheimer’s Disease and Frontotemporal Dementia Disease Modeling. Cells 2020, 9, 2018. [CrossRef]

108. Oksanen, M.; Petersen, A.J.; Naumenko, N.; Puttonen, K.; Lehtonen, S.; Gubert Olive, M.; Shakirzyanova, A.; Leskelä, S.; Sarajärvi, T.; Viitanen, M.; et al. PSEN1 mutant iPSC-Derived Model reveals severe astrocyte pathology in Alzheimer’s disease. Stem Cell Rep. 2017, 9, 1885–1897. [CrossRef] [PubMed]

109. Raut, S.; Patel, R.; Al-Ahmad, A.J. Presence of a mutation in PSEN1 or PSEN2 gene is associated with an impaired brain endothelial cell phenotype In Vitro. Fluids Barriers CNS 2021, 18, 3. [CrossRef]
110. Mestre, H.; Hablitz, L.M.; Xavier, A.L.; Feng, W.; Zou, W.; Pu, T.; Monai, H.; Murlidharan, G.; Castellanos Rivera, R.M.; Simon, M.J.; et al. Aquaporin-4-dependent glymphatic solute transport in the rodent brain. eLife 2018, 7, e40070. [CrossRef] [PubMed]

111. Nedergaard, M.; Goldman, S.A. Glymphatic failure as a final common pathway to dementia. Science 2020, 370, 50–56. [CrossRef]

112. Schwab, A.J.; Ebert, A.D. Neurite Aggregation and Calcium Dysfunction in iPSC-Derived Human Dopamine Neurons. Stem Cell Rep. 2015, 5, 1039–1052. [CrossRef]

113. Borgs, L.; Peyre, E.; Alix, P.; Hanon, K.; Grobarczyk, B.; Godin, J.D.; Purnelle, A.; Krusny, N.; Maquet, P.; Lefebvre, P.; et al. Dopaminergic neurons differentiating from LRRK2 G2019S-induced pluripotent stem cells show early neurotic branching defects. Sci. Rep. 2016, 6, 33377. [CrossRef]

114. Simon, M.J.; Patel, B.; Giralt, A.; et al. Disease-specific phenotypes in dopamine neurons from human iPS-based models of genetic and sporadic Parkinson’s disease. Proc. Natl. Acad. Sci. U. S. A. 2017, 114, 50–56. [CrossRef] [PubMed]

115. Osborn, T.; et al. Pharmacological rescue of mitochondrial deficits in iPSC-derived neural cells from patients with familial Parkinson’s disease. Sci. Transl. Med. 2012, 4, 141ra90. [CrossRef] [PubMed]

116. Sanchez-Danes, A.; Richaud-Patim, Y.; Carballo-Carbajal, I.; Jimenez-Delgado, S.; Caig, C.; Mora, S.; Di Guglielmo, C.; Ezquerra, M.; Patel, B.; Giralt, A.; et al. Disease-specific phenotypes in dopamine neurons from human iPSC-based models of genetic and sporadic Parkinson’s disease. EMBO Mol. Med. 2012, 4, 380–395. [CrossRef] [PubMed]

117. Miller, J.D.; Gatn, Y.M.; Kishinesky, S.; Bowman, R.L.; Liu, B.; Tu, E.Y.; Mandall, P.K.; Vera, E.; Sun, J.W.; Kriks, S.; et al. Human iPSC-based modeling of late-onset disease via progerin-induced aging. Cell Stem Cell. 2013, 13, 691–705. [CrossRef]

118. Sanders, L.H.; Laganiere, J.; Cooper, O.; Mak, S.K.; Vu, B.J.; Huang, Y.A.; Paschon, D.E.; Vangipuram, M.; Sundararajan, R.; Urnov, F.D.; et al. LRRK2 mutations cause mitochondrial DNA damage in iPSC-derived neural cells from Parkinson’s disease patients: Reversal by gene correction. Neurobiol. Dis. 2014, 62, 381–386. [CrossRef]

119. Schwab, A.J.; Ebert, A.D. Neurite Aggregation and Calcium Dysfunction in iPSC-Derived Sensory Neurons with Parkinson’s Disease-Related LRRK2 G2019S Mutation. Stem Cell Rep. 2015, 5, 1039–1052. [CrossRef]

120. Hsieh, C.H.; Shaltouki, A.; Gonzalez, A.E.; Bettencourt da Cruz, A.; Burbulla, L.F.; St Lawrence, E.; Schüle, B.; Krainc, D.; Palmer, T.D.; Wang, X. Functional Impairment in Miro Degradation and Mitophagy Is a Shared Feature in Familial and Sporadic Parkinson’s Disease. Cell Stem Cell. 2016, 19, 709–724. [CrossRef]

121. Mazzulli, J.R.; Zunke, F.; Tsunemi, T.; Toker, N.J.; Jeon, S.; Burbulla, L.F.; Patnaik, S.; Sidransky, E.; Marugan, J.J.; Sue, C.M.; et al. Activation of β-Glucocerebrosidase Reduces Pathological α-Synuclein and Restores Lysosomal Function in Parkinson’s Patient Midbrain Neurons. J. Neurosci. 2016, 36, 7693–7706. [CrossRef]

122. Burbulla, L.F.; Song, P.; Mazzulli, J.R.; Zampese, E.; Wong, Y.C.; Jeon, S.; Santos, D.P.; Blanz, J.; Obermaier, C.D.; Strojny, C.; et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson’s disease. Science 2017, 357, 1255–1261. [CrossRef]

123. Paillusson, S.; Gomez-Suaga, P.; Stoica, R.; Little, D.; Gissen, P.; Devine, M.J.; Noble, W.; Hanger, D.P.; Miller, C.C.J. α-Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca2+ homeostasis and mitochondrial ATP production. Acta Neuropathol. 2017, 134, 129–149. [CrossRef]

124. Neely, M.D.; Davison, C.A.; Aschner, M.; Bowman, A.B. From the Cover: Manganese and Rotenone-Induced Oxidative Stress Signatures Differ in iPSC-Derived Human Dopamine Neurons. Toxicol. Sci. 2017, 159, 366–379. [CrossRef]
132. Schwab, A.J.; Sison, S.L.; Meade, M.R.; Broniowska, K.A.; Corbett, J.A.; Ebert, A.D. Decreased Sir2/3 Deacetylase Activity in LRRK2 G2019S iPS-Derived Dopaminergic Neurons. Stem Cell Rep. 2017, 9, 1839–1852. [CrossRef]

133. Seibler, F.; Grzi佐ito, J.; Jeong, H.; Simunovic, F.; Klein, C.; Krainc, D. Mitochondrial Parkin recruitment is impaired in neurons derived from mutant PINK1 induced pluripotent stem cells. J. Neurosci. 2011, 31, 5970–5976. [CrossRef]

134. Suzuki, S.; Akamatsu, W.; Sone, T.; Ishikawa, K.I.; Kuzumaki, N.; Katayama, H.; Miyawaki, A.; Hattori, N.; Okano, H. Efficient induction of dopaminergic neuron differentiation from induced pluripotent stem cells reveals impairedmitophagy in PARK2 neurons. Biochim. Biophys. Res. Commun. 2017, 483, 88–93. [CrossRef]

135. Zambon, F.; Cherubini, M.; Fernandes, H.J.R.; Lang, C.; Ryan, B.J.; Volpato, V.; Bengoa-Vergniory, N.; Vingill, S.; Attar, M.; Booth, H.D.E.; et al. Cellular α-synuclein pathology is associated with bioenergetic dysfunction in Parkinson’s iPSC-derived dopamine neurons. Hum. Mol. Genet. 2019, 28, 2001–2013. [CrossRef]

136. Kim, J.W.; Yin, X.; Jhaldiyal, A.; Khan, M.R.; Martin, I.; Xie, Z.; Perez-Rosello, T.; Kumar, M.; Abalde-Atristain, L.; Xu, J.; et al. Detects in mRNA Translation in LRRK2-Mutant hiPSC-Derived Dopaminergic Neurons Lead to Dysregulated Calcium Homeostasis. Cell Stem Cell 2020, 27, 633–645.e7. [CrossRef]

137. Deas, E.; Cremades, N.; Angelova, P.R.; Ludtmann, M.H.; Yao, Z.; Chen, S.; Horrock, M.H.; Banushi, B.; Little, D.; Devine, M.J.; et al. Alpha-Synuclein Oligomers Interact with Metal Ions to Induce Oxidative Stress and Neuronal Death in Parkinson’s Disease. Antioxid. Redox Signal. 2016, 24, 376–391. [CrossRef]

138. Korecka, J.A.; Talbot, S.; Osborn, T.M.; de Leeuw, S.M.; Levy, S.A.; Ferrari, E.J.; Moskites, A.; Atkinson, E.; Jodelka, F.M.; Hinrich, A.J.; et al. Neurite Collapse and Altered ER Ca2+ Control in Human Parkinson Disease Patient iPSC-Derived Neurons with LRRK2 G2019S Mutation. Stem Cell Rep. 2019, 12, 29–41. [CrossRef]

139. Little, D.; Luft, C.; Mosaku, O.; Lorvellec, M.; Yao, Z.; Paillusson, S.; Kriston-Vizi, J.; Gandhi, S.; Abramov, A.Y.; Ketteler, R.; et al. A single cell high content assay detects mitochondrial dysfunction in iPSC-derived neurons with mutations in SNCA. Sci. Rep. 2018, 8, 9033. [CrossRef]

140. Tabata, Y.; Imaiuzumi, Y.; Sugawara, M.; Andoh-Noda, T.; Banno, S.; Chai, M.; Sone, T.; Yamazaki, K.; Ito, M.; Tsukahara, K.; et al. T-type calcium channels determine the vulnerability of dopaminergic neurons to mitochondrial stress in familial Parkinson disease. Stem Cell Rep. 2018, 11, 1171–1184. [CrossRef]

141. Zimprich, A.; Biskup, S.; Leitner, P.; Lichtner, P.; Farrer, M.; Lincoln, S.; Kachergus, J.; Hulihan, M.; Uitti, R.J.; Calne, D.B.; et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004, 44, 601–607. [CrossRef]

142. Liu, G.H.; Qu, J.; Suzuki, K.; Nivet, E.; Li, M.; Montserrat, N.; Yi, F.; Xu, X.; Ruiz, S.; Zhang, W.; et al. Progressive degeneration of human neural stem cells caused by pathogenic LRRK2. Nature 2012, 491, 603–607. [CrossRef]

143. Benkert, J.; Hess, S.; Roy, S.; Beccano-Kelly, D.; Wiederspoon, N.; Duda, J.; Simunovic, F.; Klein, C.; Krainc, D. Mitochondrial Parkin recruitment is impaired in neurons derived from mutant PINK1 induced pluripotent stem cells. J. Stem Cells Regen. Med. 2016, 12, 237. [CrossRef]

144. Lieberman, A.P.; Shakkottai, V.G.; Albin, R.L. Polyglutamine Repeats in Neurodegenerative Diseases. Annu. Rev. Pathol. 2019, 14, 1–27. [CrossRef]

145. Saudou, F.; Humbert, S. The Biology of Huntingtin. Neuron 2016, 89, 910–926. [CrossRef]

146. Leandro, E.; Emmanouilidou, E.; Vekrellis, K. Voltage-Gated Calcium Channels and α-Synuclein: Implications in Parkinson’s Disease. Front. Mol. Neurosci. 2019, 12, 237. [CrossRef]

147. Qian, H.; Kang, X.; Hu, J.; Zhang, D.; Liang, Z.; Meng, F.; Zhang, X.; Xue, Y.; Maimon, R.; Dowdy, S.F.; et al. Reversing a model of Parkinson’s disease with in situ converted nigral neurons. Nature 2020, 582, 550–556. [CrossRef]

148. Lieberman, A.P.; Shakkottai, V.G.; Albin, R.L. Polyglutamine Repeats in Neurodegenerative Diseases. Antioxid. Redox Signal. 2019, 30, 1450–1499. [CrossRef]

149. Czerey, M. Dysregulation of Neuronal Calcium Signaling via Store-Operated Channels in Huntington’s Disease. Front Cell Dev. Biol. 2020, 8, 611735. [CrossRef]

150. Vonsattel, J.P.; Di Fliglia, M. Huntington disease. J. Neuropathol. Exp. Neurol. 1998, 57, 369–384. [CrossRef]

151. Park, I.H.; Arora, N.; Hoo, H.; Maherali, N.; Ahfeldt, T.; Shimamura, A.; Lench, M.W.; Cowan, C.; Daley, G.Q.; Hochedlinger, K. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004, 44, 601–607. [CrossRef]

152. Zhang, N.; An, M.C.; Montoro, D.; Ellerby, L.M. Characterization of Human Huntington’s Disease Cell Model from Induced Pluripotent Stem Cells. PLoS Curr. 2010, 2, RRN1193. [CrossRef]

153. HD iPSC Consortium. Induced pluripotent stem cells from patients with Huntington’s disease show CAG-repeat-expansion-associated phenotypes. Cell Stem Cell 2012, 11, 264–278. [CrossRef]

154. Mehta, S.R.; Tom, C.M.; Wang, Y.; Bresee, C.; Rushton, D.; Mathkar, P.P.; Tang, J.; Mattis, V.B. Huntington’s Disease iPSC-Derived Cortical Neurons Display Altered Transcriptomics, Morphology, and Maturation. Cell Rep. 2018, 25, 1081–1096.e6. [CrossRef]

155. Camnasio, S.; Dellicarri, A.; Lombardo, A.; Grad, I.; Mariotti, C.; Castucci, A.; Rozell, B.; Lo Riso, P.; Castiglioni, V.; Zuccato, C.; et al. The first reported generation of several induced pluripotent stem cell lines from homoyzgous and heteroyzgous Huntington’s disease patients demonstrates mutation related enhanced lysosomal activity. Neurobiol. Dis. 2012, 46, 41–51. [CrossRef]

156. Nekrasov, E.D.; Kiselev, S.L. Mitochondrial distribution violation and nuclear indentations in neurons differentiated from iPSCs of Huntington’s disease patients. J. Stem Cells Regen. Med. 2018, 14, 80–85. [CrossRef]
181. Harmuth, T.; Prell-Schicker, C.; Weber, J.J.; Gellerich, F.; Funke, C.; Drießen, S.; Magg, J.C.D.; Krebiehl, G.; Wolburg, H.; Hayer, S.N.; et al. Mitochondrial Morphology, Function and Homeostasis Are Impaired by Expression of an N-terminal Calpain Cleavage Fragment of Ataxin-3. *Front. Mol. Neurosci.* 2018, 11, 368. [CrossRef]

182. Ouyang, S.; Xie, Y.; Xiong, Z.; Yang, Y.; Xian, Y.; Ou, Z.; Song, B.; Chen, Y.; Xie, Y.; Li, H.; et al. CRISPR/Cas9-Targeted Deletion of Polyglutamine in Spinocerebellar Ataxia Type 3-Derived Induced Pluripotent Stem Cells. *Stem Cells Dev.* 2018, 27, 756–770. [CrossRef]

183. Chen, I.C.; Chang, K.H.; Chen, Y.C.; Lee-Chen, G.J.; Chen, C.M. Pueraria lobata and Daidzein Reduce Cytotoxicity by Enhancing Ubiquitin-Proteasome System Function in SCA3-iPSC-Derived Neurons. *Oxid. Med. Cell Longev.* 2019, 2019, 8130481. [CrossRef]

184. Martier, R.; Sogorb-Gonzalez, M.; Stricker-Shaver, J.; Hübener-Schmid, J.; Keskin, S.; Klima, J.; Toonen, L.J.; Juhas, S.; Juhasova, E.; et al. Development of an AAV-Based MicroRNA Gene Therapy to Treat Machado-Joseph Disease. *Mol. Ther. Methods Clin. Dev.* 2019, 15, 343–358. [CrossRef]

185. Mendonça, L.S.; Nobrega, C.; Tavino, S.; Brinkhaus, M.; Matos, C.; Tomé, S.; Moreira, R.; Henriques, D.; Kaspar, B.K.; Pereira de Almeida, L. Ibuprofen enhances synaptic function and neural progenitors proliferation markers and improves neuropathology and motor coordination in Machado-Joseph disease models. *Hum. Mol. Genet.* 2019, 28, 3691–3703. [CrossRef] [PubMed]

186. Depla, J.A.; Sogorb-Gonzalez, M.; Mulder, L.A.; Heine, V.M.; Konstantinov, P.; van Deventer, S.J.; Wolthers, K.C.; Pajkrt, D.; Srídhár, A.; Evers, M.M. Cerebral Organoids: A Human Model for AAV Capsid Selection and Therapeutic Transgene Efficacy in the Brain. *Mol. Ther. Methods Clin. Dev.* 2020, 18, 167–175. [CrossRef]

187. García-Huerta, P.; Troncoso-Escudero, P.; Wu, D.; Thiruvaluavan, A.; Cisternas-Olmedo, M.; Henríquez, D.R.; Plate, L.; Chan-Cuevas, P.; Saquèl, C.; Thielen, P.; et al. Insulin-like growth factor 2 (IGF2) protects against Huntington’s disease through the extracellular disposal of protein aggregates. *Acta Neuropathol.* 2020, 140, 737–746. [CrossRef]

188. Thiruvaluavan, A.; de Mattos, E.P.; Brunsting, J.F.; Bakels, R.; Serlidaki, D.; Barazzuol, L.; Conforti, P.; Fatima, A.; Koyuncu, S.; Cattaneo, E.; et al. DNAJB6, a Key Factor in Neuronal Sensitivity to Amyloidogenesis. *Mol. Cell 2020, 78, 346–358.e349. [CrossRef] [PubMed]

189. Boulting, G.L.; Kiskinis, E.; Croft, G.F.; Amoroso, M.W.; Oakley, D.H.; Wainger, B.J.; Williams, D.J.; Kahler, D.J.; Yamaki, M.; Davidow, L.; et al. A functionally characterized test set of human induced pluripotent stem cells. *Nat. Biotechnol.* 2011, 29, 279–286. [CrossRef]
201. Mitne-Neto, M.; Machado-Costa, M.; Marchetto, M.C.; Bengtson, M.H.; Joazeiro, C.A.; Tsuda, H.; Bellen, H.J.; Silva, H.C.; Oliveira, A.S.; Lazar, M.; et al. Downregulation of VAPB expression in motor neurons derived from induced pluripotent stem cells of ALS patients. *Hum. Mol. Genet.* **2011**, *20*, 3642–3652. [CrossRef] [PubMed]

202. Wada, T.; Goparaju, S.K.; Tooi, N.; Inoue, H.; Takahashi, R.; Nakatsuji, N.; Aiba, K. Amyotrophic lateral sclerosis model derived from human embryonic stem cells overexpressing mutant superoxide dismutase 1. *Stem. Cells Transl. Med.* **2012**, *1*, 396–402. [CrossRef] [PubMed]

203. Egawa, N.; Kitaoka, S.; Tsukita, K.; Naitoh, M.; Takahashi, K.; Yamamoto, T.; Adachi, F.; Kondo, T.; Okita, K.; Asaka, I.; et al. Drug screening for ALS using patient-specific induced pluripotent stem cells. *Sci. Transl. Med.* **2012**, *4*, 145ra104. [CrossRef]

204. Sareen, D.; O’Rourke, J.G.; Meera, P.; Muhammad, A.K.; Grant, S.; Simpkinson, M.; Bell, S.; Carmona, S.; Ornelas, L.; Sahabian, A.; et al. Targeting RNA foci in iPS-derived motor neurons from ALS patients with a C9ORF72 repeat expansion. *Sci. Transl. Med.* **2013**, *5*, 208ra149. [CrossRef] [PubMed]

205. Alves, C.J.; Dariolli, R.; Jorge, F.M.; Monteiro, M.R.; Maximino, J.R.; Martins, R.S.; Strauss, B.E.; Krieger, J.E.; Callegaro, D.; Chadi, G. Gene expression profiling for human iPS-derived motor neurons from sporadic ALS patients reveals a strong association between mitochondrial functions and neurodegeneration. *Front. Cell. Neurosci.* **2015**, *9*, 289. [CrossRef] [PubMed]

206. Donnelly, C.J.; Zhang, P.W.; Pham, J.T.; Haeusler, A.R.; Mistry, N.A.; Vidensky, S.; Daley, E.L.; Poth, E.M.; Hoover, B.; Fines, D.M.; et al. RNA toxicity from the ALS/FTD C9ORF72 expansion is mitigated by antisense intervention. *Neuron* **2013**, *80*, 415–428. [CrossRef] [PubMed]

207. Chen, H.; Qian, K.; Du, Z.; Cao, J.; Petersen, A.; Liu, H.; Blackbourn, L.W.; Huang, C.L.; Errigo, A.; Yin, Y.; et al. Modeling ALS with iPSCs reveals that mutant SOD1 misregulates neurofilament balance in motor neurons. *Cell Stem Cell* **2014**, *14*, 796–809. [CrossRef]

208. Qu, Q.; Li, D.; Louis, K.R.; Sun, Q.; Crandall, S.R.; Tsang, S.; Zhou, J.; Cox, C.L.; et al. High-efficiency motor neuron differentiation from human pluripotent stem cells and the function of Islet-1. *Nat. Commun.* **2014**, *5*, 3449. [CrossRef] [PubMed]

209. Dafinca, R.; Scaber, J.; Ababneh, N.; Lalic, T.; Weir, G.; Christian, H.; Vowles, J.; Douglas, A.G.; Browne, C.; et al. C9orf72 Hexanucleotide Expansions Are Associated With Altered Endoplasmic Reticulum Calcium Homeostasis and Stress Granule Formation in Induced Pluripotent Stem Cell-Derived Neurons from Patients With Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. *Stem Cells* **2016**, *34*, 2063–2078. [CrossRef]

210. Bursch, F.; Kalmbach, N.; Naujok, M.; Staeger, S.; Eggenschwiler, R.; Abo-Rady, M.; Japtek, J.; Guo, W.; Hensel, N.; Reinhardt, P.; et al. Altered calcium dynamics and glutamate receptor properties in iPS-derived motor neurons from ALS patients with C9ORF72, SOD1 or TDP43 mutations. *Hum. Mol. Genet.* **2019**, *28*, 2835–2850. [CrossRef]

211. Shoukat-Mumtaz, U.; et al. A Cellular Model for Sporadic ALS Using Patient-Derived Induced Pluripotent Stem Cells. *Mol. Cell. Neurosci.* **2013**, *56*, 355–364. [CrossRef]

212. Dafinca, R.; Scaber, J.; Ababneh, N.A.; Sathyaprakash, C.; Vowles, J.; Cowley, S.A.; Reinhardt, P.; et al. C9orf72 repeat expansion causes vulnerability of motor neurons to Ca2+-permeable AMPA receptor-mediated excitotoxicity. *Nat. Commun.* **2018**, *9*, 347. [CrossRef]

213. Bursch, F.; Kalmbach, N.; Naujok, M.; Staeger, S.; Eggenschwiler, R.; Abo-Rady, M.; Japtek, J.; Guo, W.; Hensel, N.; Reinhardt, P.; et al. Altered calcium dynamics and glutamate receptor properties in iPS-derived motor neurons from ALS patients with C9ORF72, FUS, TDP43 or other mutations. *Neuron* **2017**, *96*, eaaf3962. [CrossRef]

214. Fujimori, K.; Ishikawa, M.; Otomo, A.; Atsuta, N.; Nakamura, R.; Akiyama, T.; Hotta, A.; Kondo, T.; Kitaoka, S.; Ohta, A.; et al. Modeling sporadic ALS in iPS-derived motor neurons identifies a potential therapeutic agent. *Nat. Med.* **2018**, *24*, 1579–1589. [CrossRef]

215. Osaki, T.; Uzel, S.G.M.; Kamm, R.D. Microphysiological 3D model of amyotrophic lateral sclerosis (ALS) from human iPS-derived muscle cells and optogenetic motor neurons. *Adv. Sci.* **2018**, *4*, eaat5847. [CrossRef]

216. Selvaraj, B.T.; Livesey, M.R.; Zhao, C.; Gregory, J.M.; James, O.T.; Cleary, E.M.; Chouhan, A.K.; Gane, A.B.; Perkins, E.M.; Dando, O.; et al. C9orf72 repeat expansion causes vulnerability of motor neurons to Ca2+-permeable AMPA receptor-mediated excitotoxicity. *Nat. Commun.* **2018**, *9*, 347. [CrossRef]

217. Bursch, F.; Kalmbach, N.; Naujok, M.; Staeger, S.; Eggenschwiler, R.; Abo-Rady, M.; Japtek, J.; Guo, W.; Hensel, N.; Reinhardt, P.; et al. Altered calcium dynamics and glutamate receptor properties in iPS-derived motor neurons from ALS patients with C9ORF72, SOD1 or TDP43 mutations. *Hum. Mol. Genet.* **2019**, *28*, 2835–2850. [CrossRef]

218. Dafinca, R.; Barbagallo, P.; Farrimond, L.; Candalija, A.; Scaber, J.; Ababneh, N.A.; Sathyaprakash, C.; Vowles, J.; Cowley, S.A.; Talbot, K. Impairment of Mitochondrial Calcium Buffering Links Mutations in C9ORF72 and TARDBP in iPS-Derived Motor Neurons from Patients with ALS/FTD. *Stem Cell Rep.* **2020**, *14*, 892–908. [CrossRef] [PubMed]

219. Wang, L.; Yi, F.; Fu, L.; Yang, J.; Wang, S.; Wang, Z.; Suzuki, K.; Sun, L.; Xu, X.; Yu, Y.; et al. CRISPR/Cas9-mediated targeted gene correction in amyotrophic lateral sclerosis patient iPScs. *Protein Cell.* **2017**, *8*, 365–378. [CrossRef] [PubMed]

220. Kiskinis, E.; Sandoe, J.; Williams, L.A.; Bouling, G.L.; Moccia, R.; Wainger, B.J.; Han, S.; Peng, T.; Thams, S.; Mikkilineni, S.; et al. Pathways disrupted in human ALS motor neurons identified through genetic correction of mutant SOD1. *Cell Stem Cell* **2014**, *14*, 781–795. [CrossRef] [PubMed]
222. Ichiyama, N.; Fujiyama, K.; Yano, M.; Ishihara-Fujsaki, C.; Sone, T.; Akiyama, T.; Okada, Y.; Akatsuka, M.; Matsumoto, T.; Ishikawa, M.; et al. Establishment of In Vitro FUS-Associated Familial Amyotrophic Lateral Sclerosis Model Using Human Pluripotent Stem Cells. *Stem Cell Rep.* 2016, 6, 496–510. [CrossRef] [PubMed]

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

224. Serio, A.; Bilican, B.; Barnada, S.J.; Ando, D.M.; Zhao, C.; Siller, R.; Burr, K.; Haggi, G.; Story, D.; Nishimura, A.L.; et al. Astrocyte pathology and the absence of non-cell autonomy in an induced pluripotent stem cell model of TDP-43 proteinopathy. *Proc. Natl. Acad. Sci. USA* 2013, 110, 4697–4702. [CrossRef]

225. Tyszack, G.E.; Hall, C.E.; Sibley, C.R.; Cymes, T.; Forostyak, S.; Carlino, G.; Meyer, I.F.; Schiavo, G.; Zhang, S.C.; Gibbons, G.M.; et al. A neuroprotective astrocyte state is induced by neuronal signal EphB1 but fails in ALS models. *Nat. Commun.* 2017, 8, 1164. [CrossRef] [PubMed]

226. Ferraiuolo, L.; Meyer, K.; Sherwood, T.W.; Vick, J.; Likhite, S.; Frakes, A.; Miranda, C.J.; Braun, L.; Heath, P.R.; Pineda, R.; et al. Oligodendrocytes contribute to motor neuron death in ALS via SOD1-dependent mechanism. *Proc. Natl. Acad. Sci. USA* 2016, 113, E6496–E6505. [CrossRef] [PubMed]

227. Rosen, D.R.; Siddique, T.; Patterson, D.; Figlewicz, D.A.; Sapp, P.; Hentati, A.; Donaldson, D.; Goto, J.; O’Regan, J.P.; et al. Mitochondrial Dysfunction and Calcium Dysregulation in Leigh Syndrome Induced Pluripotent Stem Cells. *Int. J. Mol. Sci.* 2022, 23, 62423.

228. DeJesus-Hernandez, M.; Mackenzie, I.R.; Boeve, B.F.; Baker, M.; Rutherford, N.J.; Nicholson, A.M.; Finch, N.A.; Flynn, H.; Adamson, J.; et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 1993, 362, 59–62. [CrossRef]

229. Sreedharan, J.; Blair, I.P.; Tripathi, V.B.; Hu, X.; Vance, C.; Rogelj, B.; Ackerley, S.; Durnall, J.C.; Williams, K.L.; Buratti, E.; et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science* 2008, 319, 1668–1672. [CrossRef]

230. Kwiatkowski, T.J., Jr.; Bosco, D.A.; Leclerc, A.L.; Tamrazian, E.; Vanderburg, C.R.; Russ, C.; Davis, A.; Gilchrist, J.; Kasarskis, E.J.; et al. Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. *Nature* 2011, 474, 19–31. [CrossRef] [PubMed]

231. Panagiotakos, G.; Haveles, C.; Arjun, A.; Petrova, R.; Rana, A.; Portmann, T.; Pašca, S.P.; Palmer, T.D.; Dolmetsch, R.E. Aberrant calcium channel splicing drives defects in cortical differentiation in Timothy syndrome. *eLife* 2019, 8, e51037. [CrossRef]

232. Krey, J.F.; Pašca, S.P.; Portmann, T.; Voineagu, I.; Yazawa, M.; Shcheglovitov, A.; Pašca, A.M.; Cord, B.; Palmer, T.D.; Chikahisa, S.; Nishino, S.; et al. Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. *Nat. Med.* 2011, 17, 1657–1662. [CrossRef]

233. Galera-Monge, T.; Zurita-Díaz, F.; Canals, I.; Hansen, M.G.; Ruffín-Vázquez, L.; Ehinger, J.K.; Elmér, E.; Martin, M.A.; Garesse, R.; Ahlenius, H.; et al. Mitochondrial Dysfunction and Calcium Dysregulation in Leigh Syndrome Induced Pluripotent Stem Cell Derived Neurons. *Int. J. Mol. Sci.* 2020, 21, 3191. [CrossRef] [PubMed]

234. Avazzadeh, S.; McDonagh, K.; Reilly, J.; Wang, Y.; Boomkamp, S.D.; McNerney, V.; Krawczyk, J.; Fitzgerald, J.; Feerick, N.; O’Sullivan, M.; et al. Increased Ca2+ signaling in NRXN1α +/- neurons derived from ASD induced pluripotent stem cells. *Mol. Autism* 2019, 10, 52. [CrossRef] [PubMed]