Genetic mouse models of Huntington’s and Parkinson’s diseases: illuminating but imperfect

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Genetic mouse models based on identification of genes that cause Huntington’s and Parkinson’s diseases have revolutionized understanding of the mechanistic pathophysiological progression of these disorders. These models allow the earliest manifestations of the diseases to be identified, and they display behavioral, neuropathological and electrophysiological deficits that can be followed over time in mechanistic and drug studies. An intriguing feature is that they do not reproduce the relatively selective and massive cell loss characterizing the human diseases. There is more information on Huntington’s disease models because the disorder involves a single gene that was identified over ten years ago; genetic mutations causing Parkinson’s disease are rare and were discovered more recently, and models of the disease have been generated only within the past few years.

Control of movement and various cognitive processes are severely affected in Huntington’s disease (HD) and Parkinson’s disease (PD), two pathologies that alter basal ganglia circuitry. HD, a dominantly inherited neurodegenerative disorder, usually begins in the fourth decade of life and is characterized by involuntary movements (chorea) and progressive cognitive decline leading to dementia. The neurons that degenerate in HD are mainly medium-sized spiny neurons (MSSNs) of the striatum [1]. The most recognizable symptoms of PD (affecting ~2% of the population over 65) include resting tremor, rigidity and bradykinesia. Although other brain regions are affected, a pathological hallmark of the disease is loss of dopaminergic neurons in the substantia nigra pars compacta.

A revolution for HD and PD research was the identification of genes that can cause these disorders. In HD, a single mutation, a CAG repeat expansion in the gene encoding the protein huntingtin, causes the disease in all patients, with full penetrance if the gene has >39 repeats [2]. Huntington’s function remains unknown. The situation is fundamentally different for PD because the disease is generally sporadic. However, the identification of several genes that cause rare familial forms has revealed pathophysiological mechanisms that might also play roles in sporadic PD. α-Synuclein, a protein altered by a mutation or gene triplication in a few families [3,4], is a major component of Lewy bodies, a characteristic neuropathological feature present in sporadic cases [5]. Similarly, parkin, a protein mutated in cases of early onset PD, is involved in proteasomal function, and recent studies in post-mortem brains have revealed a deficit in proteasomes in the substantia nigra in PD [6]. Finally, PINK1, a gene that when mutated can cause familial PD [7], encodes a mitochondrial kinase, and mitochondrial dysfunction has been reported in patients with sporadic PD [8].

Identification of disease-causing gene mutations led to the generation of mouse models. A distinct advantage of mouse models is that they permit the earliest manifestations of the mutation to be identified and progression of the disease to be studied (Figure 1). These early changes are particularly elusive in patients, and their neuropathological correlates in humans are unknown. A property of most current HD and PD genetic mouse models is the lack of robust neuronal loss. The fact that these models replicate large portions of the disease phenotype makes one wonder whether cell death is indeed necessary for symptoms to occur, and whether the symptoms represent the progressive cellular dysfunctions rather than the cell death itself.

In HD, the goal is clear and focused to a single gene, whereas in PD it is more complex because multiple genes can be affected and the contribution of genes involved in familial PD might not be similar to that in sporadic PD. Furthermore, the role of environmental factors in sporadic PD could influence genetic factors. For these reasons, information from genetic mouse models of PD has lagged behind that for HD. Because it cannot be exhaustive, this review will focus mainly on early perturbations caused by the mutations in some mouse models of HD and PD.

Huntington’s disease

Mouse models of HD include transgenics, in which a portion of the mutated gene is expressed under the control
**Figure 1.** Genetic mouse models of Huntington’s disease (HD) and Parkinson’s disease (PD). Mouse models of HD are in black text and those of PD are in red text. Abbreviations after the hyphen of the PD models indicate the promoter used in α-synuclein (αSYN) overexpressing mice. A single point indicates presence of the anomaly at that age because the model was tested at one age. An upward and/or downward arrow indicates increase and/or decrease, respectively, at that age. A continuing horizontal line indicates a change that further increases (line becoming darker) or decreases (line becoming lighter) with age; blue shading is used for HD models and gray shading for PD models. Lines of constant shading indicate that the effect does not change over time. The end of a line means that either the animals died or testing was discontinued. Numbers in brackets are references. Abbreviations: Glu, glutamate-mediated; PDGFβ, platelet-derived growth factor β; PrP, prion protein; RMP, resting membrane potential; TH, tyrosine hydroxylase; YAC, yeast artificial chromosome.

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| **Hyperactivity** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/1            |                |    |    |    |    |    |    |    |    |    |    |    |
| CAG140          |                |    |    |    |    |    |    |    |    |    |    |    |
| CAG94           |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC128          |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC72           |                |    |    |    |    |    |    |    |    |    |    |    |

| **Hypoactivity** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/1            |                |    |    |    |    |    |    |    |    |    |    |    |
| CAG94           |                |    |    |    |    |    |    |    |    |    |    |    |
| CAG140          |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC128          |                |    |    |    |    |    |    |    |    |    |    |    |
| Parkin          |                |    |    |    |    |    |    |    |    |    |    |    |
| αSYN-PDGFβ     |                |    |    |    |    |    |    |    |    |    |    |    |
| αSYN-PrP       |                |    |    |    |    |    |    |    |    |    |    |    |

| **Neuropathology** |                |    |    |    |    |    |    |    |    |    |    |    |
| **Inclusions** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2            |                |    |    |    |    |    |    |    |    |    |    |    |
| Tg100           |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/1            |                |    |    |    |    |    |    |    |    |    |    |    |
| CAG140          |                |    |    |    |    |    |    |    |    |    |    |    |
| CAG150          |                |    |    |    |    |    |    |    |    |    |    |    |
| Hdh111          |                |    |    |    |    |    |    |    |    |    |    |    |
| Hdh72,80        |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC72           |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC94           |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC128          |                |    |    |    |    |    |    |    |    |    |    |    |
| Parkin          |                |    |    |    |    |    |    |    |    |    |    |    |
| αSYN-PDGFβ     |                |    |    |    |    |    |    |    |    |    |    |    |
| αSYN-PrP       |                |    |    |    |    |    |    |    |    |    |    |    |
| αSYN-PrP       |                |    |    |    |    |    |    |    |    |    |    |    |

| **Neuronal dystrophy** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2            |                |    |    |    |    |    |    |    |    |    |    |    |
| Tg100           |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/1            |                |    |    |    |    |    |    |    |    |    |    |    |
| Hdh72,80        |                |    |    |    |    |    |    |    |    |    |    |    |

| **Neuronal loss** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2            |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC128          |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC72           |                |    |    |    |    |    |    |    |    |    |    |    |
| αSYN-PDGFβ     |                |    |    |    |    |    |    |    |    |    |    |    |

| **Decreased TH terminals** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2            |                |    |    |    |    |    |    |    |    |    |    |    |

| **Electrophysiology** |                |    |    |    |    |    |    |    |    |    |    |    |
| **RMP** |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| Input resistance |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| Ca²⁺ currents |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| Glu synaptic activity |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| GABA synaptic activity |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| Synaptic plasticity |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| NMDA responses |                |    |    |    |    |    |    |    |    |    |    |    |
| R6/2 |                |    |    |    |    |    |    |    |    |    |    |    |
| YAC72 |                |    |    |    |    |    |    |    |    |    |    |    |
| Hdh72,80 |                |    |    |    |    |    |    |    |    |    |    |    |
| Tg100 |                |    |    |    |    |    |    |    |    |    |    |    |
of various promoters, and ‘knockins’ in which an expanded CAG repeat is introduced into the endogenous mouse Huntington gene. In addition, yeast (YAC) and bacterial (BAC) artificial chromosomes have been used to express full length or portions of the mutated genes [9–11].

**Behavior**

All mouse models of HD display motor anomalies, such as hindlimb claspimg and rotarod performance disturbances, some earlier than others and some with more progression. These are not chorea but can be used as phenotypic markers ‘motor deficit’ row of Figure 1). Disease progression is particularly fast in the most frequently studied model, the R6/2 transgenic mouse, which carries exon 1 of the HD gene with ~155 CAG repeats [12]. These mice display subtle motor and learning deficits at approximately one month and overt symptoms by two months, and they usually die at three or four months [13–15]. By contrast, R6/1 mice [16] and Tg100 mice [17] have a slower progression. YAC mice with 72 or 128 CAG repeats show a biphasic motor phenotype with hyperactivity followed by hypoactivity in the open field [18,19]. A biphasic progression of behavioral anomalies also characterizes knockin mice in which human exon 1, with either 94 or 140 CAG repeats, has been inserted into the mouse Huntington gene [20,21]. The mice first show a robust increase in the number of rears when placed in an open field, followed by decreased locomotor activity. The first anomalies occur as early as one month of age in mice with the longer repeat and about one month later in mice with the shorter one, reproducing the relationship between age of onset and repeat length observed in humans [20,21]. Other knockin mice develop more subtle motor anomalies at much later ages [22,23].

**Neuropathology**

The presence of characteristic nuclear inclusions detected with antibodies against the N-terminal portion of huntingtin was first described in R6/2 mice [24]. These nuclear inclusions are present throughout the whole R6/2 mouse brain and can be detected there as early as three weeks of age [25]; they have also been described in post-mortem human HD brains [26] and in all other HD mouse models [17,24]. In knockin mice, nuclear inclusions appear late and are preceded by nuclear staining for huntingtin, followed by the presence of microaggregates of the mutant protein in the nucleus and the neuropil [20,21]. The onset of these anomalies is earlier, and their distribution broader, in CAG140 than in CAG94 mice [20,21]. Ultrastructural studies reveal many neuropil aggregates in axon terminals, which are colocalized with synaptic vesicles suggesting they might affect synaptic transmission and vesicular trafficking [27,28]. Nuclear inclusions in the various mouse models generally occur after overt behavioral anomalies, suggesting they are not solely responsible for the behavioral changes. This hypothesis is reinforced by observations that behavioral symptoms can be improved in mice without changes in inclusion load [29].

Significant changes in striatal and cortical somatodendritic morphology occur in the mouse models [17,24,30–32] (Figure 2). These can include: loss of spines; reduction of somatic areas and dendritic fields [31]; occurrence of recurving dendrites in MSSNs; and decreases in numbers of spines and dendrites, and occurrence of dystrophic dendrites, in cortical pyramidal cells [17,31]. Such features are similar to neuropathology in HD patients [1] (Figure 2). Neuronal death is not prominent in most HD mouse models, and behavioral, cognitive and neurological symptoms occur well before cell death is present [33]. In R6/2 mice, neuronal loss is modest and occurs very late in life [34]. The YAC72 and YAC128 models display the most selective degeneration of MSSNs in the lateral striatum [18,19]. Although striatal volume is reduced in older animals, knockin mice do not show evidence of cell death [20]. Thus, although HD genetic mouse models display many behavioral and neuropathological phenotypes of HD itself, they do not show marked cell loss.

**Electrophysiology**

Electrophysiological studies provide crucial information on neuronal dysfunction and circuit changes that might underlie or precede symptoms. Intrinsic membrane properties of MSSNs are affected in some of the models. Beginning at one month old, an increase in input resistance occurs in the R6/2 model [31,35], which probably reflects progressive loss of conductive membrane channels. Consistent with this observation, cell capacitance is reduced and there is decreased inward rectification. Consequently, many MSSNs have depolarized resting membrane potentials by three months [31]. There also is a progressive reduction in voltage-gated Ca^{2+} conductances beginning at two or three months [35,36].

Connections between the cortex and the striatum are also affected. Early degeneration of the corticostriatal pathway can occur in conjunction with accumulation of mutant huntingtin in axonal swellings in striatal neuropil and in the cytoplasm of cortical neurons [37,38]. Defective neurotransmission in HD also is supported by observations suggesting early impairment of proteins involved in the control of neurotransmitter release, such as a decrease in expression of complexin II, a presynaptic protein [39,40]. Abnormal phosphorylation of synapsin I predicts impairment in vesicle trafficking [41], and the abnormal association of mutant huntingtin with synaptic vesicles might impair glutamate release [42].

An early indication of electrophysiological changes along the corticostriatal pathway in R6/2 mice is the transient expression of large spontaneous synaptic inward currents at approximately one month [43]. These events could reflect dysregulation of glutamate release and/or increasing cortical synchronization. In conjunction, the frequency of low-amplitude spontaneous excitatory postsynaptic currents is progressively reduced (Figure 2), leading to an increase in the stimulus intensity necessary to evoke an excitatory postsynaptic potential in MSSNs [17,31]. This suggests the cortex might become disconnected from some of its striatal targets, depriving striatal cells of trophic factors such as brain-derived neurotrophic factor [44], and partially questions the hypothesis that chronic excess glutamate release is necessary for striatal
cell death. Either as a consequence of this disconnection or as an independent effect, GABA transmission is upregulated, suggesting compensatory mechanisms [45].

Alterations in synaptic transmission change synaptic plasticity. In several models, impairments in long-term potentiation in the hippocampus occur [15,18,46]. Less is known about changes in synaptic plasticity along the corticostriatal pathway. Paired-pulse facilitation is reduced in the R6/2 model [31]. Decreased expression of dopamine receptors, dysregulation of glutamate release and progressive reduction in synaptic activity could presage significant alterations in synaptic plasticity.

Altered receptor sensitivity or release of glutamate has been hypothesized to underlie degenerative alterations in HD. Because of the crucial role played by striatal NMDA receptors in excitotoxicity, this receptor subtype has been examined in many of the models. There is accumulating evidence that subsets of MSSNs are more sensitive to application of NMDA in virtually all models. NMDA-induced cell swelling is increased in R6/2 and the CAG94 knockin [30]. Subpopulations of MSSNs from transgenic animals display larger NMDA currents and Ca$^{2+}$ influx [17,35] and reduced Mg$^{2+}$ sensitivity [35]. Increased NMDA receptor sensitivity occurs in YAC models, and the NR2B NMDA receptor subunit is crucial for this effect [47,48].

There is considerable speculation regarding the selective vulnerability of striatal MSSNs, in particular enkephalin-containing cells. Recent evidence suggests that one has to look beyond the striatum to find the clues to neurodegeneration in HD. Alterations in synaptic transmission along the corticostratial pathway might initiate a cascade of events that eventually leads to neuronal dysfunction and cell death. Because the number of synaptic contacts can be reduced in HD, extrasynaptic glutamate receptors and their interacting proteins could play an increasingly important role. Subunit assembly is different between synaptic and extrasynaptic NMDA receptors, which have differing roles in excitotoxicity [49]. Stimulation of synaptic NMDA receptors appears to have anti-apoptotic activity, whereas stimulation of extrasynaptic NMDA receptors causes loss of mitochondrial membrane potential and cell death [50]. Enhanced activation of extrasynaptic NMDA receptors could facilitate cell dysfunction in HD.

**Therapies**

Because of its fast progression, the R6/2 model has been frequently used for preclinical drug testing in HD mice. Compounds that have been tested so far target mitochondrial function (coenzyme Q, creatine), excitotoxicity (remacemide, riluzole), aggregate formation (congo red,
trehalose), transglutaminases (cystamine), caspases (minocycline) or transcriptional dysregulation (histone deacetylase inhibitors). Several of these compounds cause either prolonged survival or delayed motor symptoms in the mice [51].

**Parkinson’s disease**

Before identification of genes causing familial forms of PD, models of the disease were limited to peripheral or local injections of neurotoxins with various degrees of selectivity for the nigrostriatal dopaminergic pathway [52]. Although these models have been invaluable in elucidating consequences of the loss of dopaminergic neurons and in developing new symptomatic therapies, their usefulness to study the progression of the pathophysiology of PD is limited because they are based on neurotoxic mechanisms whose role in sporadic PD remains speculative. Another major limitation is that these models mainly reproduce loss of nigrostriatal dopaminergic neurons. Although this is usually considered the hallmark of PD, the disease affects broad areas of the brain and peripheral organs, and pathology in non-dopaminergic regions could precede nigrostriatal cell loss [53].

Mouse models of PD based on mutations known to cause the disease in humans offer, for the first time, a way to study the full extent of PD pathology and to perform mechanistic studies. These models permit identification of early pathogenic steps in neurodegeneration, an inherently difficult task in humans [54]. A variety of transgenic and knockout mice have begun to provide information along these lines but, because these mice have only recently been developed, information lags behind that available on HD models.

**α-Synuclein**

A rare mutation in α-synuclein was the first genetic anomaly reported to cause familial PD [3]. Accumulation of α-synuclein might play a crucial role in PD because increased levels due to gene triplication can cause familial PD [4]. Mice overexpressing the normal or mutated forms of α-synuclein display a highly variable phenotype [55]. A major determinant of severity seems to be the promoter used for the transgene [56]. Most mice overexpressing α-synuclein under control of the prion promoter, and some of those overexpressing it under control of the Thy 1 promoter, display severe anomalies including massive pathology in motoneurons, which are not primarily affected in PD [57–59]. By contrast, mice overexpressing α-synuclein under control of the tyrosine hydroxylase or platelet-derived growth factor β promoters do not display motoneuron pathology [60–63]. Two such mouse lines present a neurochemical deficit in the nigrostriatal pathway and behavioral anomalies [60,63]. These mice also show α-synuclein accumulation but the full extent of the neuropathology remains to be studied. Other factors (age, environmental insults and additional genetic components) contribute to the full PD phenotype in patients. In view of the indisputable role of α-synuclein in both familial and sporadic PD, as ascertained by its accumulation in Lewy bodies, these mice provide a compelling model to investigate the role of these cytoplasmic inclusions. Furthermore, age-related loss of nigrostriatal dopaminergic neurons is accelerated in mice overexpressing α-synuclein, an effect that is worsened by exposure to pesticides [64].

**Parkin**

A second type of mutation that causes familial parkinsonism occurs in the gene encoding parkin, an E3 ligase [65]. Many different mutations have now been described in parkin and they account for a large proportion of early-onset PD, although they are also found, more rarely, in cases with late onset [6]. Because Lewy bodies are generally absent in the brain of patients with parkin mutations, these mutations might not cause bona fide PD. However, a defect in proteasomal function has been detected in the substantia nigra in sporadic PD, thus linking the pathophysiological mechanisms of sporadic PD and forms of the disease caused by parkin mutations [6]. Because parkin mutations are loss-of-function, and most are recessive, models have focused on parkin knockout mice. In a quaking mouse mutant with a spontaneous deletion of the parkin gene, the principal CNS neuropathology is myelin deficiency and elevated dopamine metabolism. These mice also have behavioral deficits and tremor in the caudal part of the trunk and extremities [66]. Parkin knockout mice with a defective exon 3 show progressive motor anomalies when crossing a transverse beam, as well as deficits in sensorimotor integration, starting as early as two to four months of age. Paradoxically, they have increased basal release of striatal dopamine, and reduced synaptic striatal neuronal excitability [67]. Similar deficits are observed in another line of mice with a comparable mutation [68]. Neither line, however, displays clear loss of dopaminergic neurons. Therefore, similar to α-synuclein overexpressing mice, parkin knockout mice do not reproduce the full spectrum of anomalies observed in patients, especially the loss of nigrostriatal dopaminergic neurons. However, these models show clear sensorimotor anomalies. Furthermore, the parkin knockout mice display decreased levels of proteins involved in mitochondrial function and oxidative stress in the substantia nigra [69]. The PINK1 mutation also involves oxidative stress [7]. Thus, these models offer an opportunity to elucidate the earliest anomalies caused by parkin mutations, which could eventually lead to dopaminergic neuronal degeneration. Such abnormalities might occur in humans long before clinical diagnosis.

**Concluding remarks**

The usefulness of genetic models is invaluable and the seminal multidisciplinary work promises a very exciting future for understanding the pathophysiological mechanisms of HD and PD progression, and for devising new avenues for treatment. From HD and PD models, we have learned that neuronal dysfunction occurs before overt behavioral symptoms appear and, for that same reason, one might have a reasonable hope to treat and even reverse neurodegeneration and symptoms. Despite this promising beginning, none of the models replicates the massive cell loss of striatal and dopaminergic neurons occurring in humans with these diseases. Although we do not yet know why cell loss is not prominent, the
information gleaned has begun to provide clues. Much remains to be done to create mechanistically significant, full models of each disease. New genetic approaches need to be tried and, in the case of PD, a combination of insults to mimic more closely the environment in which the disease develops in humans will be insightful. Several new mutations have been discovered in PD patients [6], and others will probably be elucidated in the near future. It is likely that PD mouse models soon will be used to test therapies based on an emerging understanding of the pathophysiology of PD, as is already the case for HD.

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