# Manganese-Induced Dopaminergic Neurodegeneration: Insights into Mechanisms and Genetics Shared with Parkinson's Disease

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## 1. Introduction

Manganese (Mn) is an abundant, naturally occurring element in the Earth's crust. It is most frequently found in the form of oxides, carbonates, and silicates.[1] It is also one out of seven essential metals for animal physiology. Mn is a cofactor for many enzymes, such as transferases, hydrolases, lyases, arginase, glutamine synthetase, and superoxide dismutase, and it is also found in integrins.[2,3] The well-studied Mn-containing proteins are arginase, an enzyme present in lipids that is required for ammonia elimination, and Mn-containing superoxide dismutase (Mn-SOD), a principal antioxidant enzyme typically found in the mitochondria. Given the dependence of multiple enzymes on Mn, it is essential for various physiological processes, such as modulation of the immune system, stellate process production in astrocytes, cell adhesion, and protein and carbohydrate metabolism.[4−8] Mn also plays an important role in the development and functioning of the brain and skeletal structures.[9,10] Mn deficiency may result in birth defects, poor bone formation and increased susceptibility to seizures.[11,12]

Despite being essential for metabolic functions, excessive exposure to Mn is a well-recognized occupational hazard, and inhalation of particulate Mn compounds is associated with lung inflammation, characterized by cough, bronchitis, pneumonitis, and impaired pulmonary function in human, primates,[13−19] and nasal epithelium inflammation in rodents.[20] Impotence and loss of libido have also been reported in male workers with high Mn exposures,[21,22] possibly due to the importance of arginase in those functions.[23] Though most Mn is obtained through the diet, Mn toxicity from dietary intake is rare,[24,25] because Mn balance is tightly regulated by both the enterocytes (intake) and the biliary duct cells (excretion). In contrast, pulmonary uptake and particulate transport via the olfactory bulb[26−28] can lead to deposition of Mn within the striatum and cerebellum, and inflammation of the nasal epithelium.[20] Occupational exposure to Mn for periods from 6 months to 2 years can cause an extrapyramidal syndrome, referred to as manganism, closely resembling idiopathic Parkinson's disease (IPD, see below), at both the molecular and clinical levels.[29−31] Manganism represents a progressive Parkinsonism syndrome with a dystonic gait disorder ("cock gait"). Patients suffering from manganism exhibit a signature biphasic mode of physical decline, which comprises of an initial phase of psychiatric disturbance including rare cases of emotional lability, and neurological deficits which are followed by motor defects such as akinetic rigidity, dystonia, and bradyskinesia.[29,31] Mn exposure represents a significant public health matter due to the use of Mn as a catalyzer in countless

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industrial processes and to its presence in gasoline additives, in fungicides such as Maneb, and in permanganate, a drinking water purifier.[1,2,32−35] Moreover, Mn toxicity may be liable for some PD cases, which are on the rise.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that currently affects nearly 2% of the U.S. population.[36] In most populous countries, more than 4 million individuals over 50 had PD in 2005, and this number is expected to reach 9 million by 2030.[37] Clinically, PD patients classically display four signature symptoms: rigidity, tremor, dystonia, and bradykinesia, and occasionally akinesia. Physiologically, these symptoms result from a progressive loss of motor function due to the degeneration of the dopaminergic (DAergic) neurons within the substantia nigra pars compacta and the loss of DAergic terminals in the striatum.[38] At the subcellular level, postmortem studies revealed the deposition of cytoplasmic Lewy bodies composed of aggregated protein, including α-synuclein. Epidemiology studies classify PD cases as familial (FPD) or IPD, depending on whether the disease is hereditary (FPD) or from unknown origin, possibly due to exposure to environmental neurotoxicants (IPD).[39,40] Eleven genomic regions (PARK1 to 11) have been associated with FPD. For eight of these, responsible genes have been identified: PARK1 (α-SYNUCLEIN), PARK2 (PARKIN), PARK4 (α-SYNUCLEIN), PARK5 (UCHL1), PARK6 (PINK1), PARK7 (DJ1), PARK8 (DARDARIN/LRRK2), and PARK9 (ATP13A2).[41] On the other hand, various environmental contaminants were suspected in IPD cases, especially pesticides, such as paraquat and rotenone, and metals such as lead (Pb) and Mn.

Interestingly, those usual suspects in IPD and the aforementioned genes identified in FPD impact the same signaling pathways involved in mitochondrial function, oxidative stress, and cell death. This observation underlines the importance of gene−environment interaction studies for the understanding of neurodegenerative diseases such as PD. In the case of Mn, it is in fact the only environmental toxicant that has been robustly associated with IPD, it tends to accumulate in the same brain areas that are affected in PD, and it can induce a syndrome closely resembling PD, as mentioned previously. Recent studies also suggest the direct involvement of Mn exposure in PD's etiology.[42] Here, we survey the similarities between PD and Mn neurotoxicity, focusing on the cellular pathways common to both disorders and PD genes identified thus far. Since gene−environment studies are presently amenable to high-throughput approaches in various *in vivo* genetic models, we report here recent insights into the etiology of PD and Mn toxicity gained from various model organisms, and we explore the conservation of PD genes across species. A central point of this review is reflected in the theme that most molecular and mechanistic aspects of both Mn-associated disorders and PD are conserved across species from *C. elegans* to humans, justifying the utility of *C. elegans* and other invertebrate models for further characterization of gene x environment interactions in the etiology of neurodegenerative disorders.

## 2. Conserved Mechanisms in Parkinson's Disease and Manganism

### 2.1. PD and Mn-Induced DA Neuron Degeneration

The brain areas most susceptible to manganese (Mn) injury are also highly sensitive to oxidative stress. Many metabolically active cell types, particularly tonically active motor neurons in the substantia nigra (SN), require high levels of ATP for optimal function and survival.[43] Mn accumulates in the SN, globus pallidus (GP), and striatum (STR), where it interferes with ATP synthesis, in a similar fashion to mitochondrial inhibitors or experimentally induced ischemia.[44−49] The accumulation of Mn in these brain regions corresponds to highly dense expression of the divalent metal transporter 1 (DMT1),[50−53] which has been found to be responsible for dietary[54,55] as well as olfactory[28] Mn uptake.[53] Both for PD and Mn-induced neurodegeneration, the dopaminergic (DAergic) neurotransmitter system is primarily affected in human,[30,56−59] nonhuman primates,[60,61] and rodents,[62−74] as well as in *C. elegans* (unpublished data). Though the mechanisms that lead to Mn-induced neurodegeneration are still poorly understood, multivalent metallic ions in general and $Mn^{2+}$ and $Mn^{3+}$ in particular are able to react with biogenic amines (such as dopamine) through the Fenton's reaction and produce reactive-oxygen species (ROS), leading to oxidative damage.[66,67,75−77] Several mechanisms for Mn-catalyzed dopamine (DA) auto-oxidation have been proposed, involving semiquinone and aminochrome intermediates, L-cysteine or copper (Cu), and NADH facilitation.[62,67,76,78−81] Our recent work with *C. elegans* further supports a direct role for DA metabolism in Mn-induced DAergic neurodegeneration (unpublished data). The specificity of Mn accumulation conferred by DMT1 and its ability to react with DA may explain the selective targeting of DAergic neurons in Mn-induced Parkinsonism.

The DAergic system is also particularly sensitive to other oxidants in addition to metals.[82−85] DA is the first neurotransmitter system to undergo neuronal cell loss upon brain oxidative injury and energy depletion.[86,87] Accordingly DAergic cell loss can be partially prevented by various antioxidants in *in vivo* and *in vitro* PD models.[88−103] The mechanisms responsible for the primary loss of DAergic neurons in PD are not fully elucidated and most likely involve the deregulation of DA metabolic pathways and glutamate excitotoxicity. However, the commonalities between manganism and PD do not solely rely on the loss of DAergic neurons. Appraisal of the literature strongly suggests the DAergic neurodegeneration associated with PD and Mn exposure share multiple molecular mechanisms, namely mitochondrial dysfunction, energy depletion, aberrant signal transduction, oxidative stress, protein aggregation, and the activation of necrotic and apoptotic cell death pathways.

### 2.2. Mitochondria and Oxidative Stress in PD and Mn-Induced DAergic Neurodegeneration

#### 2.2.1. Oxidative metabolism in PD and PD models

Postmortem studies of PD patients demonstrate chemical changes indicative of reactive oxygen/nitrogen species-induced damage to the SN. Such changes include increased levels of lipid peroxidation, protein oxidation, 3-nitrotyrosine formation, DNA oxidation, DNA breaks, and a decrease in the activities of the ROS scavenging enzymes, glutathione peroxidase and superoxide dismutases. Several hypotheses propose that mitochondrial damage is a primary cause of the DAergic neuronal death observed in PD. They suggest that: (1) mitochondria of DAergic neurons are selectively vulnerable to environmental contaminant(s) which causes mitochondrial dysfunction; (2) DAergic neurons produce an endogenous mitochondrial toxin; or (3) mitochondria harbor defects in enzymes or protein complexes, such as complex-I, that lead to impaired energy metabolism. The centrality of mitochondria in these hypotheses arise primarily from findings that mitochondrial poisons such as 1-methyl-4-phenylpyridium ions ($MPP^+$) [the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)] and rotenone can induce a Parkinsonian-like syndrome in humans, nonhuman primates, and rodents. These neurotoxins are all capable of inhibiting mitochondrial complex-I and appear to model the pathology of PD. Neuropathological studies reveal ~30% decrease in complex-I function in deceased PD patients, as compared with age-matched controls.

The mitochondrial complex-I inhibitors, MPTP/MPP+ and rotenone (model toxins for PD), damage nigral neurons by mechanisms involving oxidation.[104] Oxidative damage also plays a significant role in 6-OHDA-induced DAergic neuronal cell death. $H_2O_2$, superoxide ions, and hydroxyl radicals[105] generated by nonenzymatic breakdown of 6-OHDA or by the direct inhibition of complex-I activity, lead to lipid peroxidation, protein denaturation, and a decrease in glutathione (GSH), which are postmortem hallmarks of PD[106−108] (Figure 1A). Another well studied source of oxidative injury to the mitochondria in various PD models is the aforementioned glutamate excitotoxicity. Calcium influx via *N*-methyl-D-aspartate excitatory amino acid receptors (NMDAR) induces an increase in mitochondrial ROS generation, mitochondrial depolarization, and apoptosis.[109−113]

#### 2.2.2. Mn Toxicity and Oxidative Stress

There are many similarities between the aforementioned features of PD and Mn-induced neurotoxicity. Intracellular $Mn^{2+}$ is sequestered by mitochondria via the $Ca^{2+}$ uniporter[114−117] (Figure 1A). Intrastriatal Mn injections result in loss of DAergic neurons, resembling toxicity caused by the mitochondrial poisons, aminooxyacetic acid and $MPP^+$.[118] Oxidative stress plays a significant role in this process[119−121] (Figure 1A). MPTP-induced DAergic neurodegeneration involves glutamate-mediated toxicity; noncompetitive or competitive NMDA antagonists protect nigral neurons from this effect.[122,123] Mn has also been shown to increase *in vivo* synaptic glutamate concentrations, leading to excitotoxic and oxidative injury.[118] Analogous to $MPP^+$ and 6-OHDA, Mn elevates intracellular $H_2O_2$ and related peroxides[124] and reduces tyrosine hydroxylase (TH)[66,125−130] as well as intracellular antioxidant (GSH, thiols, catalase) activities in DAergic neurons.[130,131] Consistent with increased production of ROS, Mn inhibits mitochondrial complex-I, a feature inherent to PD and PD-mimicking drug treatments ($MPP^+$, 6-OHDA, rotenone, or paraquat treatments).[131] Both $MPP^+$ and Mn activate heme oxygenase-1,[126] whose overexpression promotes oxidative mitochondrial damage.[132] It has been proposed that the effects of Mn on oxidative stress are dependent on its oxidation state and are more pronounced for Mn in the 3+ (vs 2+) oxidation state.[133,134] A link between mitochondrial impairment, oxidative stress, and increased α-synuclein aggregation is well documented for

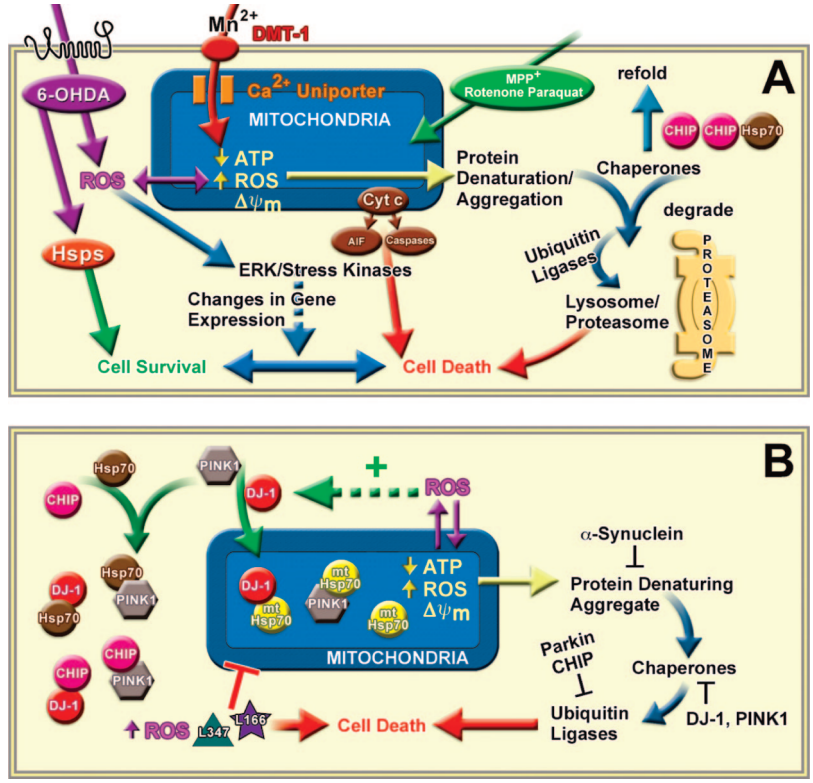


**Figure 1.** Intracellular pathways involved in dopaminergic neurodegeneration. (A) Molecular pathways associated with oxidant-induced DAergic cell death by Mn. (B) The potential role of DJ-1, PINK1, their respective mutants, L166 and L347, and chaperones (HSP70, CHIP, and mtHSP70) in DAergic cell death. Please refer to the text for additional detail.

Mn and various PD models.[135−138] Studies have also confirmed that treatment with Mn in a pre-Parkinsonian state (mimicked by 6-OHDA treatment) significantly exacerbates neurobehavioral impairment in the rat. This not only suggests that Mn exposure may increase the risk of injury in subpopulations that are in a preparkinsonism state, but it also points to the convergence of signaling pathways that lead to such injury[139] (Figure 1A).

## 2.3. Cell Death Mechanisms in PD and Mn-Induced DAergic Neurodegeneration

### 2.3.1. Apoptosis and Necrosis

Whether classical apoptosis or necrosis plays a role in DAergic neurodegeneration in PD has been debated.[140−142] Models of toxin-induced PD implicate both apoptosis and necrosis, depending on the particular type of toxin, animal, or culture system used. Studies with DA or 6-OHDA suggest an apoptotic form of cell death, while treatments with $MPP^+$/MPTP and the pesticide rotenone induced both apoptotic and necrotic cell death.[143−150] Microarray gene expression studies do not report significant changes in apoptotic gene expression in response to Mn exposure, although marginal DNA laddering and caspase activity have been noted.[131,151,152] These findings do not exclude changes in translational mechanisms that could activate apoptosis.

As discussed above, deficits in complex-I stimulate intramitochondrial oxidative stress, in turn increasing the releasable soluble pool of cytochrome *c* within the mitochondrial intermembrane space (Figure 1A). Analogous to experimental models of PD ($MPP^+$, 6-OHDA, rotenone), Mn (as MMT) effectively induces mitochondrial cytochrome *c* release[153] (Figure 1A). In the process, Mn, 6-OHDA, and $MPP^+$ activate identical caspases (caspase-1, -3, and -7).[124] Proteolytic activation of the proapoptotic PKCδ is a key mediator of 6-OHDA-induced cell death. Cell death is mediated via caspase 3-dependent cleavage of full-length PKCδ, and inhibition of PKCδ attenuates neurotoxicity.[154] MMT-induced cell death is also associated with proteolytic cleavage of PKCδ, and the effects of MMT, $MPP^+$, and 6-OHDA are suppressed by treatment with the caspase inhibitors, Z-VAD-FMK and Z-DEVD-FMK. Thus, caspase-3 mediates the proteolytic activation of PKCδ in multiple models of PD-associated DAergic neurodegeneration.[153,155,156]

### 2.3.2. Brief Considerations on Age-Related Effects

Oxidative stress and mitochondrial impairment leading to cell death are not specific to manganism or PD-associated neurodegeneration, as they naturally occur with aging.[157] Aging is associated with mitochondrial iron overload,[158,159] respiratory chain oxidative damage,[160] and activity decrease,[161,162] increase in free radical production,[163,164] decrease in antioxidant response[165−168] and DNA-repairing abilities,[169,170] and increased oxidation of lipids,[171] proteins,[172−176] and nucleic acids.[177] This sensitive state of the aging brain makes it more vulnerable to heavy-metal-induced oxidative stress[178−180] or other injuries, such as seizures.[181] Similarly, it probably explains the prevalence of PD in elderly people.[182] However, PD and manganism can affect younger individuals as well, due to hereditary conditions (early onset FPD) or chronic occupational exposure to high Mn doses. In these cases, the cause of the syndrome likely reflects perturbation of specific common genetic determinants.

## 3. PD Genes and Mn Toxicity

### 3.1. Genes Implicated in PD: Genetic and Association Studies

Genetic association studies have identified a small collection of genes that are involved in up to 7% of PD cases.[183,184] The discovery of mutations in α-synuclein,[185] *PARKIN*,[186] *UCH-L1* (ubiquitin carboxy-terminal hydrolase L1),[187] *DJ-1*,[188] *NR4A2* or *NURR1* (NUR-Related factor 1),[189] *PINK1* (PTEN-INduced Kinase 1),[190] and *LRRK2*[191] provides a framework for much of the ongoing molecular research in PD. Although most of these genes are implicated in only a small percentage of all PD cases, they nevertheless provide insight into disease mechanisms, potential treatments, and gene−environment interactions in the pathogenesis of PD.

#### 3.1.1. PARK1/PARK-4/α-Synuclein

α-Synuclein is a presynaptic protein that associates with synaptic vesicles and participates in excitation−secretion coupling.[192−197] α-Synuclein is involved in the regulation of both DA biosynthesis and DA transporter (DAT) function.[193,198] PD-associated coding mutations (A30P and A53T) in α-synuclein alter its structure and precipitate aggregate formation and Lewy body deposition,[199−201] reducing DAergic neuron viability.[200−202] α-Synuclein is normally degraded by a proteosomal pathway[203] (Figure 1B) and by a lysosomal pathway mainly involving cathepsin D, casein kinase 2.[204−209] Genetic screens in yeast also identified factors involved in α-synuclein degradation for both the ubiquitin/proteasome pathway and the vacuolar degradation pathway (equivalent of the lysosomal route in yeast).[210,211] Other studies support a link between oxidative damage and formation of α-synuclein aggregates, a known feature of PD.[212,213] Consistent with observations in *Drosophila melanogaster*, transgenic (tg) mice overexpressing human wild-type (wt) or mutant α-synuclein exhibit neurodegeneration, motor deficits, and abnormal cellular accumulation of α-synuclein aggregates.[198,200,214−216] This suggests factors that control selective DAergic vulnerability are evolutionarily conserved. In general, α-synuclein mutations sensitize cells to oxidative events, and α-synuclein itself is a target for oxidative modifications, such as nitrosylation.[212] *In vitro* aggregation of α-synuclein is dramatically accelerated by 6-OHDA treatment.[217,218]

The nematode *Caenorhabditis elegans* (*C. elegans*) does not normally express α-synuclein. However, overexpression of wild type (wt) human α-synuclein in *C. elegans* increases vulnerability to mitochondrial complex-I inhibitors (rotenone, fenperoximate, pyridaben, and stigmatellin), which is reversed by treatment with antioxidants.[219] Transgenic worms overexpressing mutant A30P or A53T human α-synuclein in DAergic neurons show accumulation of α-synuclein in the cell bodies and neurites of these neurons.[201] Concurrently, the neuronal DA content is reduced, altering DAergic neuron function and worm behavior, which is rescued by administration of dopamine.[201] Moreover, MPTP/MPP+ exposure leads to behavioral defects and a specific degeneration of DAergic neurons in wt worms.[220] A genome-wide expression screen comparing wt and mutant α-synuclein-expressing worms further identified 500 genes with significant expression change between the two strains.[221] Recently, a *C. elegans* study confirmed that α-synuclein is involved in synaptic vesicle recycling and that the endocytic pathway plays a role in α-synuclein neurotoxicity.[222] As observed in mammalian models, neuroprotectants, such as acetaminophen, were proven efficient in attenuating DAergic neuronal loss in the nematode.[223] Finally, interfering RNA in worms overexpressing human α-synuclein revealed 20 genes potentially involved in α-synuclein age-dependent aggregation and PD.[224] Though *C. elegans* does not exhibit PD, those findings emphasize its relevance as a model organism to gain rapid insights in the genetic pathways involved in PD and to apply high-throughput screening methods to search for new anti-PD drugs.[225−228]

#### 3.1.2. PARK-2/Parkin

Mutations in PARKIN are associated with early onset PD (<30 years) and are the most frequent cause of the recessive forms of PD. The *parkin* gene encodes an E3 ubiquitin ligase,[229] suggesting that failure to modify specific cellular targets with ubiquitin may cause DAergic neuronal cell death (Figure 1A). In PARKIN-associated PD there is a loss of DAergic neurons, but Lewy bodies are generally not present. PARKIN is neuroprotective *in vitro* and is up-regulated upon oxidative stress.[230] In multiple transgenic animal models, PARKIN overexpression effectively attenuates α-synuclein aggregation;[229,231−234] however, the neuroprotective properties of PARKIN against apoptosis are independent of protein aggregation.[235] Fly *parkin* null mutants exhibit degeneration of DAergic neurons and mitochondrial pathology and are sensitive to ROS generating metals (such as Fe),[236−239] suggesting that PARKIN functions to protect cells from oxidative stress, likely by controlling the degradation of oxidized or damaged proteins.[240] Parkin also upregulates PINK1,[241] and compelling recent evidence supports an intricate role of PINK1 in mitochondrial morphogenesis and physiology (see section 3.1.4).

Unlike α-synuclein, PARKIN is very well conserved in *C. elegans*, where it is encoded by the gene *pdr-1* (Figure 2). Deleting[242] or knocking-down *pdr-1* in *C. elegans* produces similar patterns of pharmacological vulnerability to those described above for overexpression of α-synuclein.[219]

#### 3.1.3. PARK-5/UCH-L1

UCH-L1 (Ubiquitin C-terminal Hydrolase-L1) is a ubiquitously expressed enzyme that catalyzes the hydrolysis of C-terminal ubiquitinyl esters. It may be involved in recycling ubiquitin attached to misfolded proteins after their degradation by the proteasome.[243] This function may also be involved in autoregulation through deubiquitination of monoubiquitylated UCH-L1.[244] In addition to its deubiquitination role, UCH-L1 would act as an ubiquitin-ligase upon dimerization.[245] UCH-L1 up-regulation is a hallmark of invasive breast cancer[246] and may have an antiproliferative role,[247] probably by promoting apoptosis, as seen in mouse spermatogenesis.[248,249] UCH-L1 also protects against protein aggregation disorders such as Alzheimer's disease[250,251] and probably PD. A dominant missense mutation affecting a weakly conserved residue (I93M, Figure 3) in UCH-L1 seems responsible for inherited PD in one German family, though no clinical data is reported.[187] A significant number of studies reported a protective effect of the S18Y polymorphism against PD.[252−257] Nevertheless, UCH-L1 mutations were never found in other PD patients[252,258−260] and the protective effect of the S18Y polymorphism is still contested.[261−265] It has also been postulated that S18Y might be associated

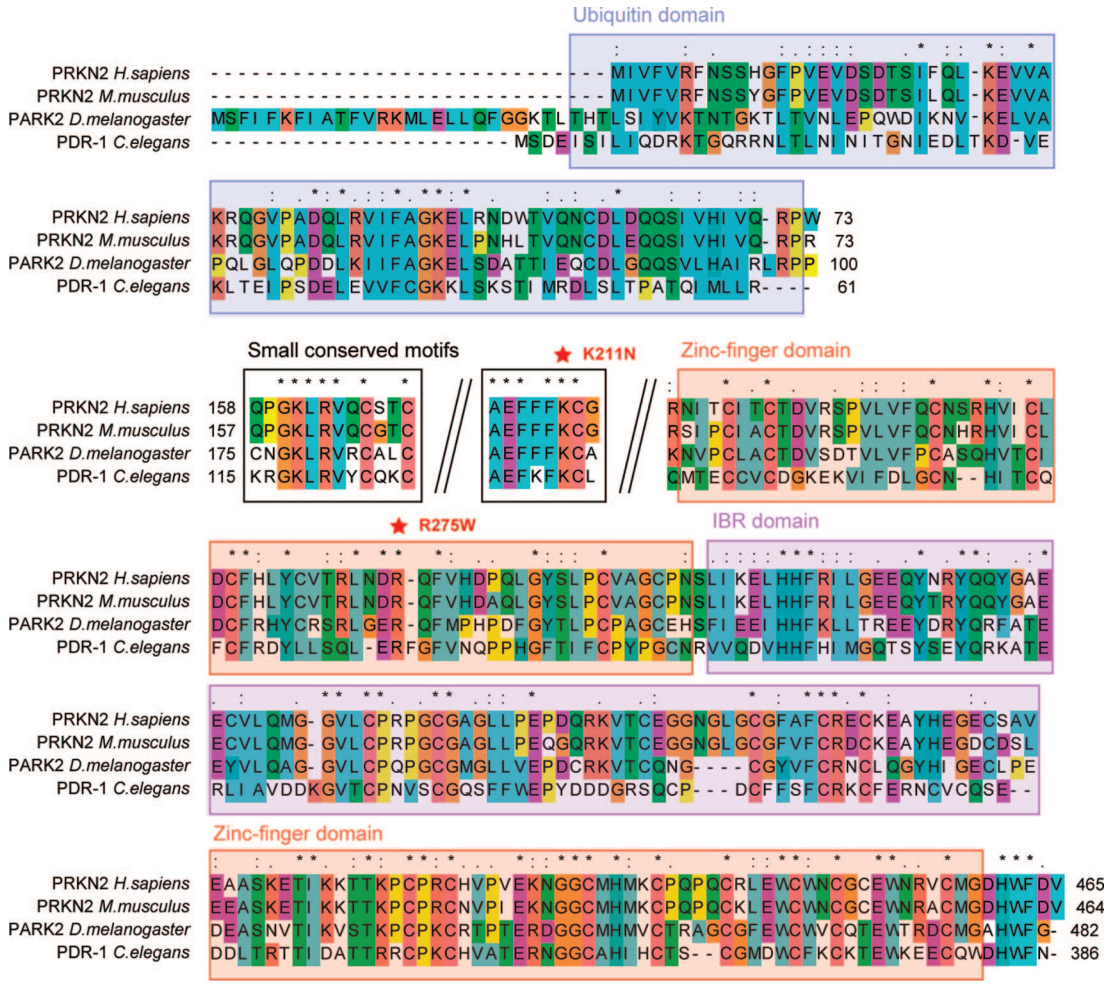


**Figure 2.** Multiple-alignment of the PARKIN/PARK2 protein domains from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. Parkin is an E3 ubiquitin protein ligase from the RBR protein family, containing an ubiquitin domain (blue) and two RING/Zinc-finger domains (red) separated by a conserved IBR domain (In Between Ring, purple). The two mutations reported in the juvenile 2 form of Parkinson's disease (K211N and R275W) affect residues highly conserved across species, including the nematode *C. elegans*. All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

with increased risk of Huntington's disease.[266] Down-regulation of UCH-L1 was reported for patients with dementia with Lewy Bodies (DLB) but did not occur in PD patients.[267] In mice, I93M decreases UCH-L1 activity but does not result in any DAergic neuron degeneration, and it affects axons of neurons originating from the dorsal root ganglia.[268]

However, overexpression of the wt UCH-L1 in mice leads to DAergic neuron degeneration, and DAergic neurons of transgenic mice for the I93M-mutated form are more sensitive to MPTP treatment.[269] UCH-L1 overexpression also leads to protein inclusion formation, where it colocolizes with ubiquitylated proteins, HSP70 and $\gamma$-tubulin, and is found in inclusions together with Parkin and α-synuclein.[270] Moreover, mutant mice lacking UCH-L1 expression accumulate $\beta$- and $\gamma$-synucleins,[271] enforcing the idea that UCH-L1 may be important in preventing aggregation of ubiquitylated proteins. It has recently been shown that UCH-L1 regulates neuronal progenitor morphology *via* an ubiquitin-dependent activity and not via its hydrolase function.[272] Consistently, I93M decreases whereas S18Y increases UCH-L1 ubiquitin-ligase activity.[245] Interestingly, Parkin, α-synuclein, and the UCH-L1 ubiquitin-ligase activity could act together in the formation of lysine 63-linked conjugates, which target proteins for endolysosomal sorting and/or degradation.[273] Low levels of UCH-L1 are also associated with lysosomal storage disorders and may account for increased apoptosis associated with these diseases.[274] A recent report shows that UCH-L1 interacts with LAMP-2A (lysosome-associated membrane protein 2A), Hsc70, and Hsp90, and it may be involved in chaperone-mediated autophagy of α-synuclein.[275] A new form of membrane-bound farnesylated UCH-L1 was recently uncovered, which may be involved in the inhibition of α-synuclein lysosomal degradation.[276] Finally, it is postulated that UCH-L1 plays a role in synaptic activity independent of its hydrolase function.[277]

Given its critical function in cell biology, it is not surprising to find that UCH-L1 is conserved across eukaryotes and *a fortiori* in *C. elegans*. However, neither the I93M nor S18Y substitutions affect highly conserved residues (Figure 3). The worm's genome encodes 3 UCH-L1/3 isoforms organized in operons (thus most probably transcribed together) UBH-1, UBH-2, and UBH-3 exhibiting 32%−40% identity with human UCH-L1 and UCH-L3. UCH-L3 and UCH-L1 are very closely related and partially redundant in human,[246,278−283] raising the possibility that

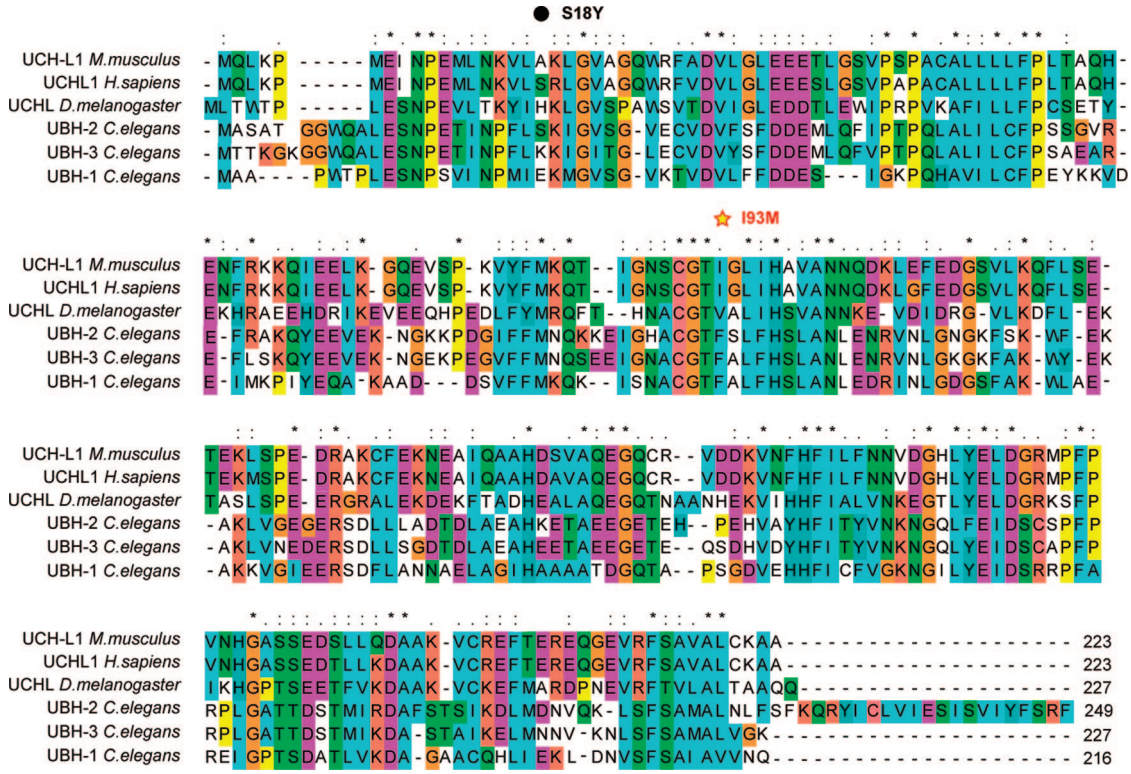


**Figure 3.** Multiple-alignment of the UCHL1/PARK5 protein sequences from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. UCH-L1 (Ubiquitin Carboxyl-Terminal HydroLase, family 1) has three orthologues in *C. elegans*, which are closely related to UCH-L3: UBH-1, UBH-2, and UBH-3. Though the UCH-L1 sequence is conserved from human to worm, mutations thought to provide susceptibility to (I93M) or protection against (S18Y) Parkinson's disease (PD) affect nonconserved residues. All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

UCH-L3, which is down-regulated in PD patients,[267] could be involved in PD. Like human UCH-L1/3, both UBH-1 and UBH-3 in *C. elegans* showed C-terminal hydrolase activity toward ubiquitin and NEDD8.[284] In addition, UBH-1 is required in neurons responsible for egg-laying and defecation, as shown in the *ubh-1(tm256)* mutant,[284] while *ubh-2* has yet to be studied.

### 3.1.4. PARK-6/PINK1

*pink1* is a recently discovered causative gene of parkinsonism and the first protein directly linking mitochondrial abnormalities to a PD phenotype. *pink1* is transcriptionally trans-activated by the PTEN protein. Human PINK1 (PTEN-INduced Kinase 1) encodes a highly conserved, 581-amino acid, putative serine/heroine protein kinase, and is a member of a small family of novel kinase including CLIK1 (CLP-36 interacting kinase)/PDLIM1 kinases. The amino-terminus of PINK1 is a mitochondrial-targeting sequence,[285] but the topology of PINK1 suggests that its kinase activity is exerted in the cytosol.[286] Overexpressed, epitope-tagged PINK1 localizes to mitochondria (Figure 1B) and offers protection against cell death, but a recessive mutant PINK1 fails to do so.[190] The substrates of PINK1 have yet to be identified, but it appears that phosphorylation of PINK1 substrates controls some critical function for neuronal survival. Two very promising candidates are Cdc37 and Hsp90, which at least *in vitro* can bind PINK1 and affect its subcellular localization, as well as its 66 kDa to 55 kDa isoform ratio.[287] Moreover, the L347P PINK1 substitution, which is associated with PD and drastically reduces its kinase activity and neuroprotective properties,[285] prevents PINK1 interaction with Cdc37 and Hsp90.[288] However, recent evidence suggests that PINK1 directly phosphorylates Parkin and controls its mitochondrial localization, which may explain its antagonistic roles.[289] Overexpression of wt PINK1, but not mutant PINK1, strongly suppresses both basal and staurosporine-induced caspase-3 activity and reduces the levels of cleaved caspase-3, caspase-7, caspase-9, and activated poly(ADP-ribose) polymerase under basal and staurosporine-induced conditions.[290,291] PINK1 also protects against α-synuclein toxicity in *Drosophila*[292] and against DAergic neurodegeneration induced by MPP+ treatment in mammalian cells.[293] Conversely, loss of PINK1 leads to increased oxidative stress, to increased α-synuclein aggregation, to proteosomal and mitochondrial dysfunction,[294−296] and to developmental defects and neurodegeneration in zebrafish.[297] In the past 2 years, PINK1 has been proposed to prevent cell death by inhibiting mitochondrial permeability transition pore (mPTP) opening,[298] by regulating mitochondrion fission together with Parkin[299,300]

*C. elegans* PINK1 (PINK-1) is encoded by the gene *pink-1*. The overall protein shares 60% similarity with mammal PINK1, with a better conservation at the level of the conserved kinase domain (Figure 4). Though ten of the human PINK1 substitutions associated with PD affect residues conserved in *C. elegans* PINK-1, only a single study on *pink-1* has been carried out thus far.[301] Confirming previous observations, PINK-1 seems to play a role in mitochondrion physiology, as mitochondrial cristae are

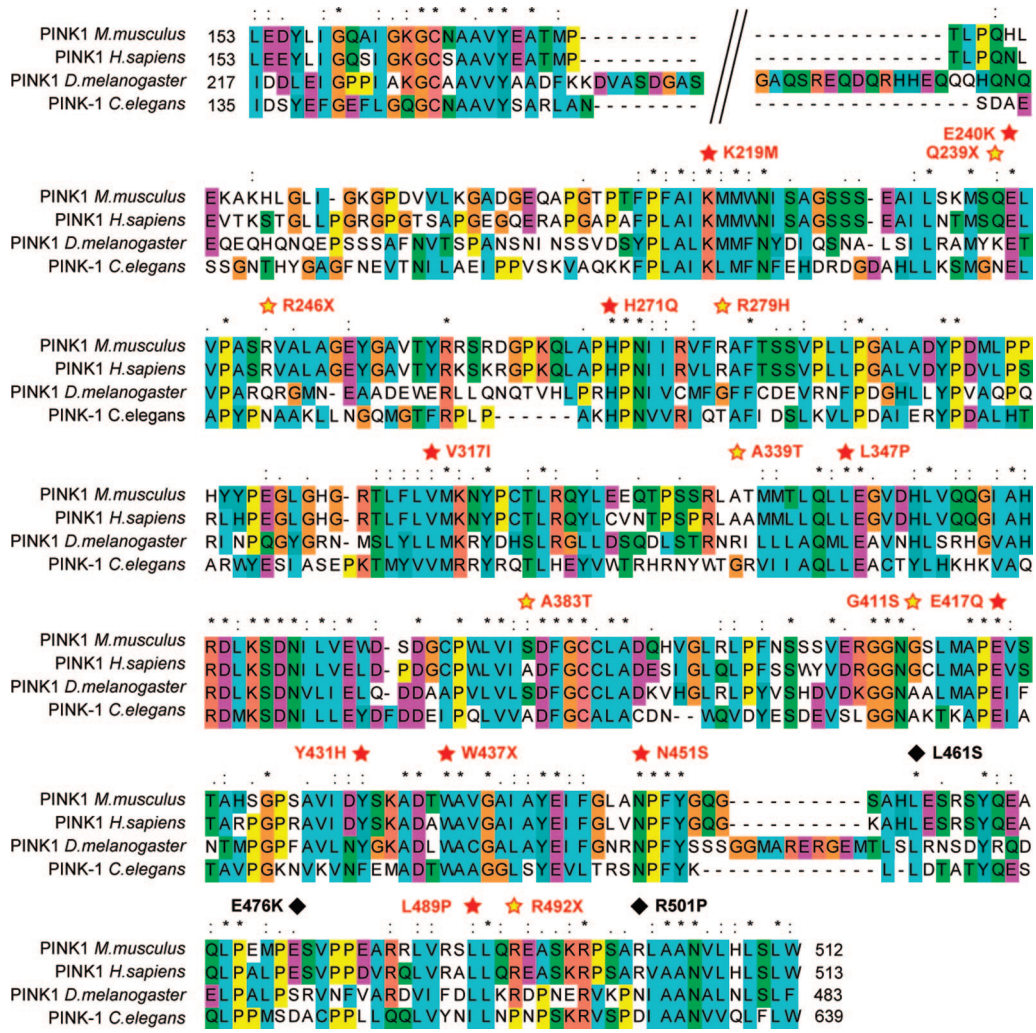


**Figure 4.** Multiple-alignment of the PINK1/PARK6 kinase domain from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. Seventeen human missense mutations in the PINK1 (PTEN-INduced Kinase 1) kinase domain were associated with PD (stars), among which 10 affect residues conserved in *C. elegans* (red stars) and 7 affect poorly conserved residues (yellow stars). Three asymptomatic mutations are also reported and concern residues in domains of less conservation (dark lozenges). All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

shortened in a *pink-1* worm mutant and the latter is more sensitive to paraquat toxicity, a mitochondrial inhibitor.[301]

### 3.1.5. PARK-7/DJ-1

The human *dj-1* gene has seven exons and encodes 189 amino acids (20 kDa).[302] DJ-1 is part of the DJ-1/ThiJ family, which includes prokaryote and eukaryote kinases[303] and thus contains a conserved kinase domain (Figure 5). Mutations in *DJ-1* are linked to an autosomal recessive early onset PD and cause familial PD, which represents 1−2% of all early onset cases.[304,305] A number of pathogenic mutations have been identified in *DJ-1* causing exonic deletions, truncations, duplications, and homozygous (M26I, E64D, E163K, and L166P) and heterozygous (R98Q, A104T, and D149A) missense mutations.[304−310] DJ-1 is a regulatory subunit of an RNA-binding protein complex.[311] Interestingly, DJ-1 has been identified as a hydroperoxide-responsive protein which plays an essential role in oxidative stress responses[312,313] and DAergic neuroprotection.[314] It was more recently identified as a peroxiredoxin-like peroxidase.[315] In response to oxidative stimuli, the gene product is converted into a more acidic variant, which can be cleaved by ROS[316] and relocated to the mitochondria, where it protects neurons from apoptosis[317] (Figure 1B). It is believed that ROS are eliminated by oxidizing DJ-1 itself. Functional knockdown of DJ-1 with RNAi results in cellular accumulation of ROS, oxidative stress, and DAergic neurodegeneration.[235] Inactivation of a *Drosophila dj-1* homologue (*dj-1*α) leads to impairment in the oxidative stress response and in phosphatidylinositol 3-kinase (PI3K)/Akt signaling.[235] Altered PI3K/Akt signaling is also inherent to the fly *parkin* model, pointing to a potentially common molecular event and intersecting pathways in the pathogenesis of PD.[235] After its localization into mitochondria, DJ-1 also maintains complex-I activity against bisphenol A-induced oxidative stress.[318] Consistently, *dj-1*α and *dj-1β* knockdowns in *Drosophila* are more vulnerable to mitochondrial complex-I inhibitors and are rescued by antioxidants.[235] Mice deficient in DJ-1 exhibit hypo-locomotion when subjected to amphetamine challenge and increased striatal oxidative stress and DAergic neurodegeneration upon MPTP treatment. Restoration of DJ-1 expression mitigates these effects.[319] In the rat DA cell line N27 and in primary DAergic neurons, overexpression of wt DJ-1 protects cells from $H_2O_2$- and 6-OHDA-induced cell death. Additionally,

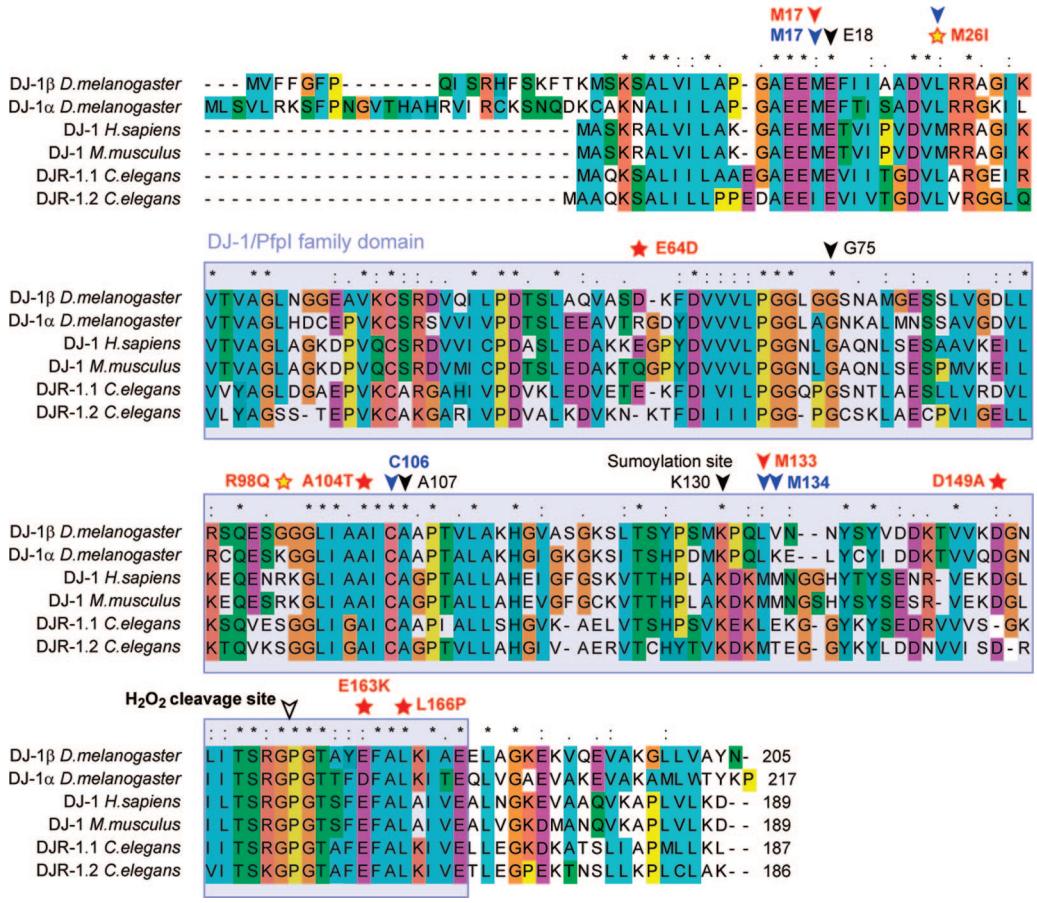


**Figure 5.** Multiple-alignment of the DJ-1/PARK7 protein sequences from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. The residues affected by the mutations E64D, A104T, D149, E163K, and L166P in PD patients are conserved at least in one of the two *C. elegans* DJR-1 isoforms, and the Met residues are susceptible to sulfonation in PD patients (M17 and M133). The C106 residue, which is oxidized to C106-$SO_2H$ upon oxidative stress, the interacting residues E18, G75, A107, and H126, as well as the K130 site of sumoylation are conserved in all DJ-1/DJR-1 isoforms, though neither Met residues 26 and 134 nor R98 appear strongly conserved. All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

DJ-1 is required for astrocyte-driven neuroprotection.[320] Overexpression of the L166P mutant of *dj-1* proffers no protective effect, and knocking down endogenous *dj-1* renders cells more susceptible to ROS.[321] Unlike DJ-1, it is believed that the mutant gene product, L166P, (1) is not translocated to the mitochondria in a pro-oxidant environment, effectively reducing protection from oxidative stress,[322] and (2) promotes loss of cytoplasmic function by virtue of the dramatically destabilized mutant DJ-1 protein.[323]

DJ-1 is a transcriptional coactivator[311,324,325] but also shares structural analogy with Hsp31 and prevents α-synuclein aggregation, which indicates a probable chaperone activity.[326] Both functions depend on its oxidation at C106 that is required for its relocation to the mitochondria.[317] DJ-1 activity may also be modified by reversible or irreversible methionine oxidation, respectively, into methionine sulfoxide (blue arrows in Figure 5) and methionine sulfone (red arrows in Figure 5)[327] and by cleavage by ROS between the two conserved residues G157-R158.[316] Additionally, DJ-1 binds Ubc9 and SUMO-1 in a yeast two-hybrid system and its sumoylation on K130 is essential for normal activity, whereas L166P pathogenic DJ-1 encounters multiple aberrant sumoylation.[328] Recent results suggest that DJ-1, together with Parkin and PINK1, forms an E3 ubiquitin-ligase complex that may be involved in α-synuclein degradation.[329]

Although two slightly divergent isoforms of DJ-1 exist in invertebrates (DJ-1$\beta$ and 1α in *D. melanogaster*, and DJR-1.1 and 1.2 in *C. elegans*), its protein sequence is very well conserved across the animal kingdom. Noticeably, most substitutions associated with human PD target residues are conserved in at least one of the two DJR-1 isoforms (Figure 5), making *C. elegans* an interesting model with which to study the intracellular consequences of these mutations.

### 3.1.6. PARK8/LRRK2/Dardarin

lrrk2 (Leucine-Rich Repeat Kinase 2)/Dardarin was cloned as the causative gene for the PARK8 adult-onset autosomal-dominant form of familial PD.[191,330] At least 25 missense mutations (A211V, K544E,[331] P755L,[332,333] R793M,[334] Q930R,[335] R1067Q,[336] S1096C,[335] L1122V,[330] S1228T,[335] I1122V,[330] L1165P,[334] I1371V,[337] R1441C,[330,338] R1441G,[191] R1441H,[339] R1514Q,[340] R1628P,[341] Y1699C,[191,330] M1869T,[342] R1941H,[343] I2012T,[344] G2019S,[345−347] I2020T,[330] T2356I,[343] and G2385R[348,349]) have been identified in about 7% of patients with familial[350] or sporadic PD.[344,351,352] Among those, G2019S appears to be the most common variant.[335,353−360] So far, mutations in *lrrk2* are the most common cause of autosomal-dominant inherited parkinsonism,[361] both early and late-onset,[362] familial, and idiopathic

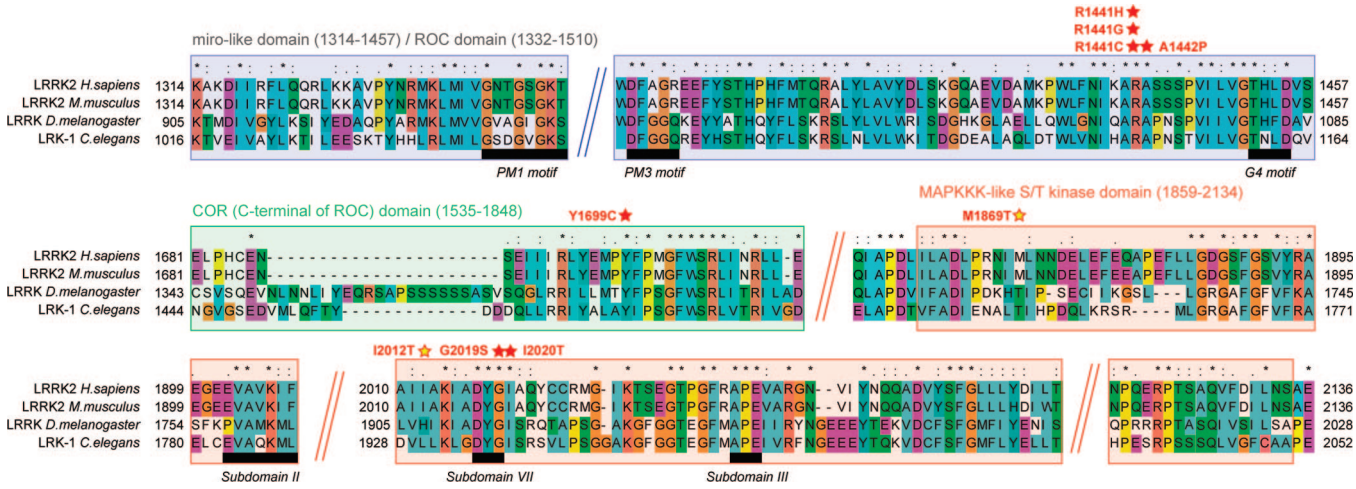


**Figure 6.** Multiple-alignment of conserved ROC and kinase domains of LRRK2/PARK8 from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species[#]. LRRK2 (Leucine-Rich Repeat Kinase 2) is a long protein of more than 2500 amino acids whose functional domains are well conserved across animal species, here exemplified by parts of the ROC (blue box), COR (green box), and kinase (red box) domains. Specific conserved subdomains in the GTPase family (PM1, PM3, and G4 motifs) and the MAPKKK (Mitogen-Activated Protein Kinase Kinase Kinase) family are indicated by black boxes. Mutations reported in PD patients are shown by stars ahead of the human protein sequence. Those affecting conserved residues in the *C. elegans* orthologue LRK-1 are emphasized by red stars, whereas others are indicated by yellow stars. All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

PD.[363−365] Furthermore, mutations in *lrrk2* are mostly specific to PD[366,367] and induce a gradual loss of DAergic neurons detectable by positron emission tomography (PET) in asymptomatic patients.[368]

The *lrrk2* gene encompasses 51 exons encoding a 2527 amino acid and a 286 kDa protein. LRRK2 harbors two protein−protein interaction regions: an N-terminus Leucine-Rich Repeats and Ankyrin repeats region and a C-terminal WD40 domain. Additionally, it contains a tandem GTP-binding ROC domain (Ras Of Complex protein) that is related to the miro-like domain found in MItochondrial RhO GTPases, and a kinase domain highly similar to the MAPKKK one. This set of domains identifies LRRK2 as a member of the strongly conserved but poorly known ROCO protein family.[369,370] LRRK2 is ubiquitously expressed, although at low levels. In particular, it is active in the developing adult mouse and rat brains, notably in the striatum,[371,372] and preferentially in DAergic neurons.[373] It is mainly distributed within the cytoplasm, and it binds the C-terminal RING-finger domain of Parkin through the COR domain.[374] Wt and mutant forms of LRRK2 were associated with lipid-rafts in the Golgi apparatus, with the plasma membrane, and in synaptic vesicles of mouse primary neurons.[375] Endogenous LRRK2 was found in Lewy Bodies.[376,377] Coexpression of both Parkin and wt LRRK2 enhances protein inclusions and ubiquitination of aggregating proteins in culture cells.[374] Additionally, mutant LRRK2 (R1441C, Y1699C, G2019S) induce neuronal degeneration in primary neuron cultures.[374]

Though LRRK2 pathogenic mutations were found in all the LRRK2 protein domains,[378] different studies suggest that the mechanism leading to PD involves modifications of the kinase function of LRRK2. Hence, the pathogenic variant I2020T shows increased kinase activity,[379] and "kinase-dead" variants protect cells against inclusion body formation and cell death.[380] Moreover, the MAPK pathway proteins Src, HSP27, and JNK are hypophosphorylated in leucocytes isolated from LRRK2-G2019S variant carriers.[381] Further investigation of LRRK2-G2019S in neurons also revealed that autophagy is likely involved in its pathogenicity.[382] The ROC domain does not possess GTPase activity but allows GTP binding, which is required for the kinase activity,[369] microtubule binding,[383] and LRRK2 homodimerization.[384,385] Noticeably, the most frequent pathogenic substitutions affecting the GTP-binding domain (R1441X) and the active site of the kinase domain (G2019S and I2020T, Figure 6)[378] occurred several times, independently across human recent evolution.[191,330,386,387] Hence, most pathogenic forms of LRRK2 affect indirectly (R1441X) or directly (G2019S, I2020T) the kinase activity, which is further supported by recent biochemical and pharmacological studies.[388,389] This suggests that *in fine* the modification of kinase activity is responsible for the toxicity of most LRRK2 mutations. Accordingly, mutations in protein−protein interaction domains would compromise association with substrates, regulators, coactivators, or proteins that are responsible for the correct localization of LRRK2. Potential interactors of LRRK2 include chaperone proteins such as HSP-90 and midasin, clathrin heavy chain, vimentin, kinases, and factors that are involved in protein translation.[379,380,390] In addition, LRRK2 could be involved in programmed cell death through Fas-Associated with Dead Domain (FADD) protein and caspase-8 signaling.[391] Based on its biochemical and genetic interactions with Rab5b, LRRK2 has also been proposed to act in synaptic vesicle endocytosis.[392] Recent microarray analysis in a LRRK2 RNAi system showed expression changes in genes involved in axonal guidance, nervous system development, cell cycle, cell growth, cell differentiation, cell communication, MAPKKK cascade, and Ras protein signal transduction.[393] Interestingly, despite its versatility, LRRK2 does not appear to be essential for *Drosophila* development but may contribute to oxidative-stress resistance.[394,395]

The LRRK2 protein sequence is well conserved across metazoans, and residues mutated in confirmed pathogenic human variants (R1441X, A1442P, G2019S, I2020T) are

conserved in the *C. elegans* orthologue LRK-1 (Figure 6). LRK-1 was found in the Golgi apparatus of neurons, where it is involved in the sorting of synaptic vesicle (SV) proteins.[396] Two subsets of SV are differentially secreted to the axon (thanks to an AP-1/UNC-101 associated machinery) or to the dendrites (thanks to a kinesin/UNC-104). Precisely, LRK-1 allows the proper targeting of SV proteins to the axon, by excluding them from the dendrite-specific transport machinery.[396] It has also been shown that in *C. elegans* LRK-1 antagonizes PINK-1 activity, given that *lrk-1* mutation rescues all *pink-1* defects.[301]

#### 3.1.7. PARK9/ATP13A2

*PARK9* is one of the last chromosomal regions associated with FPD.[188,397] Several association studies confirmed its role in Parkinsonism and autosomal recessive early onset PD.[398−403] However, in a recent study reporting 37 new variants from Tunisian families affected by FPD, no correlation was found either with FPD or with IPD.[404] Other studies did not find any association with Parkinsonism−dementia amyotrophic lateral sclerosis (ALS)[405] or late-onset PD.[406] *PARK9* was recently mapped to the gene *ATP13A2*, encoding a P-type ATPase of the P5 subfamily, with unknown substrate or function.[407] P5 P-type ATPases are a highly conserved family of transporters from worms to human, among which Atp13a2 was found ubiquitously expressed in mice[408] with a predominant expression in neurons.[407] Subcellularly, wt Atp13a2 was localized to lysosomes, while truncated mutant protein was retained in the endoplasmic reticulum (ER), pending further degradation by the proteasome.[407] Atp13a2 was also found on Lewy body-like inclusions in $\beta$-synuclein mutated neuroblastoma cells.[209] More recently, yeast genetics and PD models of α-synuclein overexpression in cultured DAergic neurons and in *C. elegans* demonstrated that Atp13a2 and its orthologues protect cells against α-synuclein overexpression and misfolding.[211] The conservation of Atp13a2 is remarkable from invertebrates to human, as shown in Figure 7.

#### 3.1.8. Other PARK Proteins

Thus far, PARK3 and PARK10 have not been cloned and therefore correspond to unidentified proteins whose conservation in *C. elegans* remains unknown. PARK11 was originially identified as the Grb10-Interacting GYF Protein-2 (GIGYF2/TNRC15) gene, with 7 different mutations of the gene identified in PD patients.[409] However, other studies suggest otherwise,[410−412] with PARK11 associated with a PD-related disease, referred to as Dementia with Lewy Bodies (DLB).[413] Several recent studies also developed various genetic strategies (using bioinformatics and genetic models such as *S. cerevisiae* and *C. elegans*) to identify new PD-associated loci and proteins, yielding promising candidates that require further investigation.[211,224,414−416]

### 3.2. The Role of Chaperone Proteins in PD

#### 3.2.1. HSP70

PD is associated with accumulation of abnormal polypeptides followed by their aggregation. It is thus logical to assert that chaperones, ubiquitin-proteasome systems, and other protein degradation systems must play a role in protection against disease progression. Among molecular chaperones, representatives of the HSP70 (Heat-Shock Protein of 70 kDa) family are the most frequent components of α-synuclein aggregation products.[417] There is consensus that increased production of chaperones is beneficial, attenuating aggregation of toxic proteins and disease development. In support of this assertion, HSP70 overexpression in multiple experimental models dramatically reduces α-synuclein-associated loss of neurons, and conversely, inhibition of HSP70 activity aggravates toxicity.[418−420] HSP70 is likely to suppress cell death signaling events caused by aggregating abnormal proteins and preserves survival pathways, but the exact mechanisms have yet to be delineated. Another means for HSP70 chaperones to limit neurodegeneration is to protect mitochondria from oxidative damage. HSP70 is highly conserved in *C. elegans* in which it is encoded by the hsp-1 gene (Figure 8). Among the HSP70 family, mitochondrial HSP70 (mtHSP70) is believed to protect neurons against oxidative stress, notably upon ischemic injury.[421]

#### 3.2.2. CHIP (C-Terminus of Hsp70 Interacting Protein)

CHIP has also been implicated in degradation of PD-associated proteins. It binds to both HSP70 and HSP90 and possesses E3 ubiquitin ligase activity toward substrates recognized by chaperones[422] (Figure 1B). CHIP is highly expressed in the central nervous system (CNS). It colocolizes with α-synuclein and is a component of Lewy bodies. In a cell culture model, overexpression of CHIP inhibits α-synuclein inclusion formation and reduces α-synuclein protein levels.[423] Similarly, CHIP upregulation attenuates aggregation of tau,[424] another component of Lewy bodies. CHIP acts as a cochaperone, directing the degradation of misfolded α-synuclein via either a tetratricopeptide repeat domain-dependent proteosomal pathway or a U-box-dependent lysosomal pathway, thus controlling the balance of aggregation/degradation of misfolded α-synuclein. CHIP is conserved across eukaryotes, and its essential functional domains are present in *C. elegans* orthologues (Figure 9).

#### 3.2.3. HSP90

Similarly to HSP70, HSP90 has been found to protect neurons from thermal injury, ischemia, protein aggregation, and apoptosis.[425−433] HSP90 is also found on cellular inclusions resulting from protein aggregation in various neurodegenerative disorders, including PD.[434−437] Unlike HSP70 chaperones, which tend to direct misfolded proteins to degradation, HSP90 ones protect their targets from degradation.[438] Hence, HSP70 and HSP90 can act antagonistically, with HSP70 affording protection while HSP90 accelerates damage, such as in polyglutamine-mediated neurodegeneration,[439−441] amyloid beta toxicity,[442] and PD. The HSP90 inhibitor geldanamycin (GA) induces an overexpression of HSP70 and protects against MPTP-induced DAergic toxicity.[443,444] HSP90 is also effective in protecting neurons from apoptosis via inhibition of caspase activity.[429] Finally, HSP90 has been shown to exert antioxidant effects in glial cells.[445] Similar to other chaperon proteins, HSP90 is highly conserved across the animal kingdom down to *C. elegans*, in which it is called DAF-21 (Figure 10). *daf-21* mutants were initially isolated due to their ability to constitutively form stress-resistant larval forms of *C. elegans* called dauer. DAF-21 is also involved in chemosensation together with the guanylyl-cyclase DAF-11,[446] which regulates DAF-7/TGF-$\beta$.[447] Additionally, *daf-21* is required for *C. elegans* immunity[448] and the extended life span of the

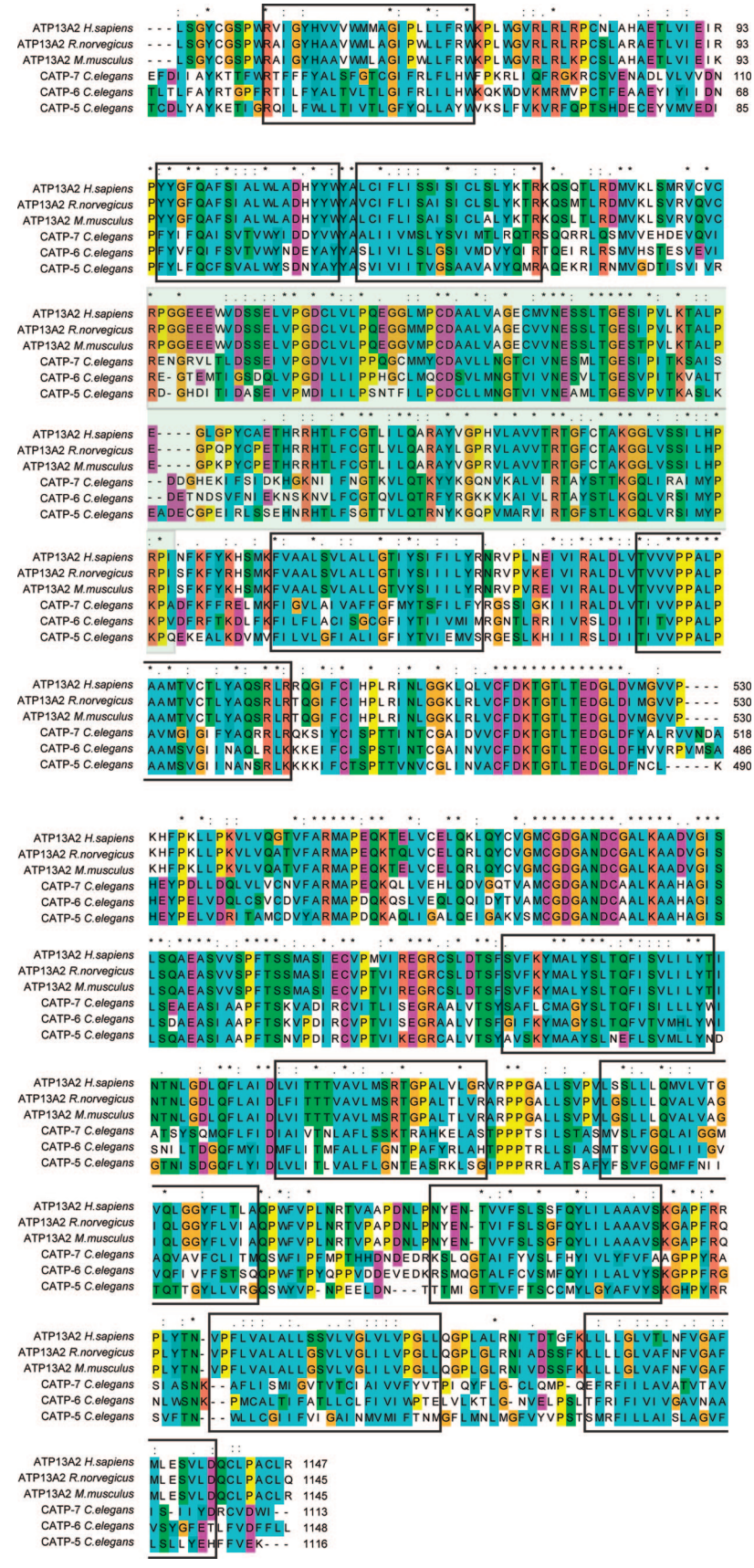


**Figure 7.** Multiple-alignment of conserved ATP13A2/PARK9 domains from human (*H. sapiens*), mouse (*M. musculus*), rat (*R. norvegicus*), and worm (*C. elegans*) species. ATP13A2 belongs to the class V P-type ATPases that is a well conserved protein family of calcium pumps. There are three ATP13A2-related *C. elegans* orthologues which display the same topology (conserved transmembrane domains are indicated by black boxes) and calcium P-type ATPase domain (light green box). All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

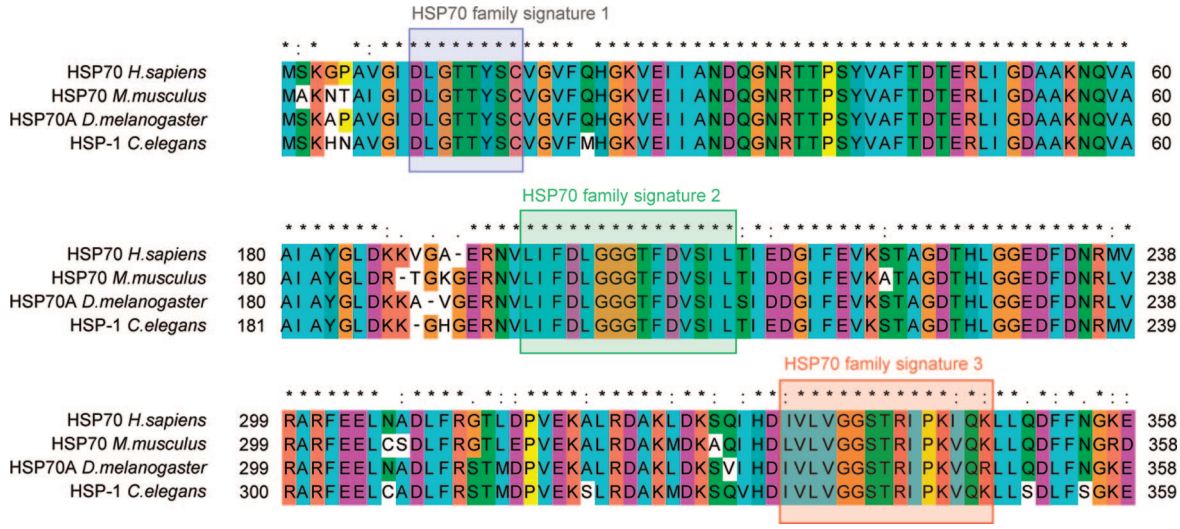


**Figure 8.** Multiple-alignment of the conserved HSP70 domain from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. HSP70 (Heat-Shock Protein of 70 kDa) is a highly conserved chaperone protein in eukaryotes whose sequence is almost perfectly conserved between human and worm. Typical signature domains of the HSP70 protein family are indicated by blue, green, and red boxes. All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

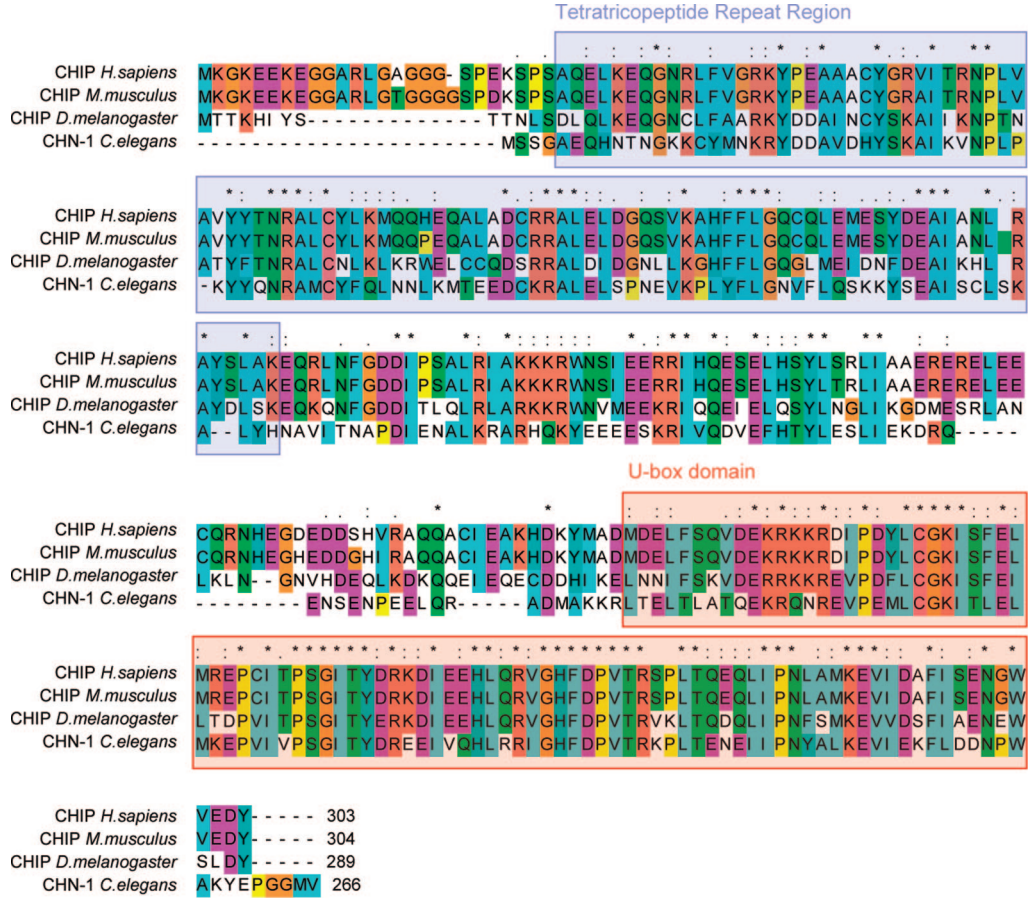


**Figure 9.** Multiple-alignment of the CHIP protein from human (*H. sapiens*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. CHIP is a chaperone associated E3 ubiquitin ligase which contains two main domains: a tetratricopeptide region allowing protein−protein interactions and a U-box domain allowing E3 ubiquitin ligase activity. Both domains are well conserved in the *C. elegans* orthologue CHN-1. All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

*age-1 C. elegans* mutants.[449] Interestingly, *daf-21* mutants display enhanced abnormal protein aggregation upon bacterial infection, and this effect is reduced by antioxidants.[450] The *C. elegans Hsp90/daf-21* thus provides a link between

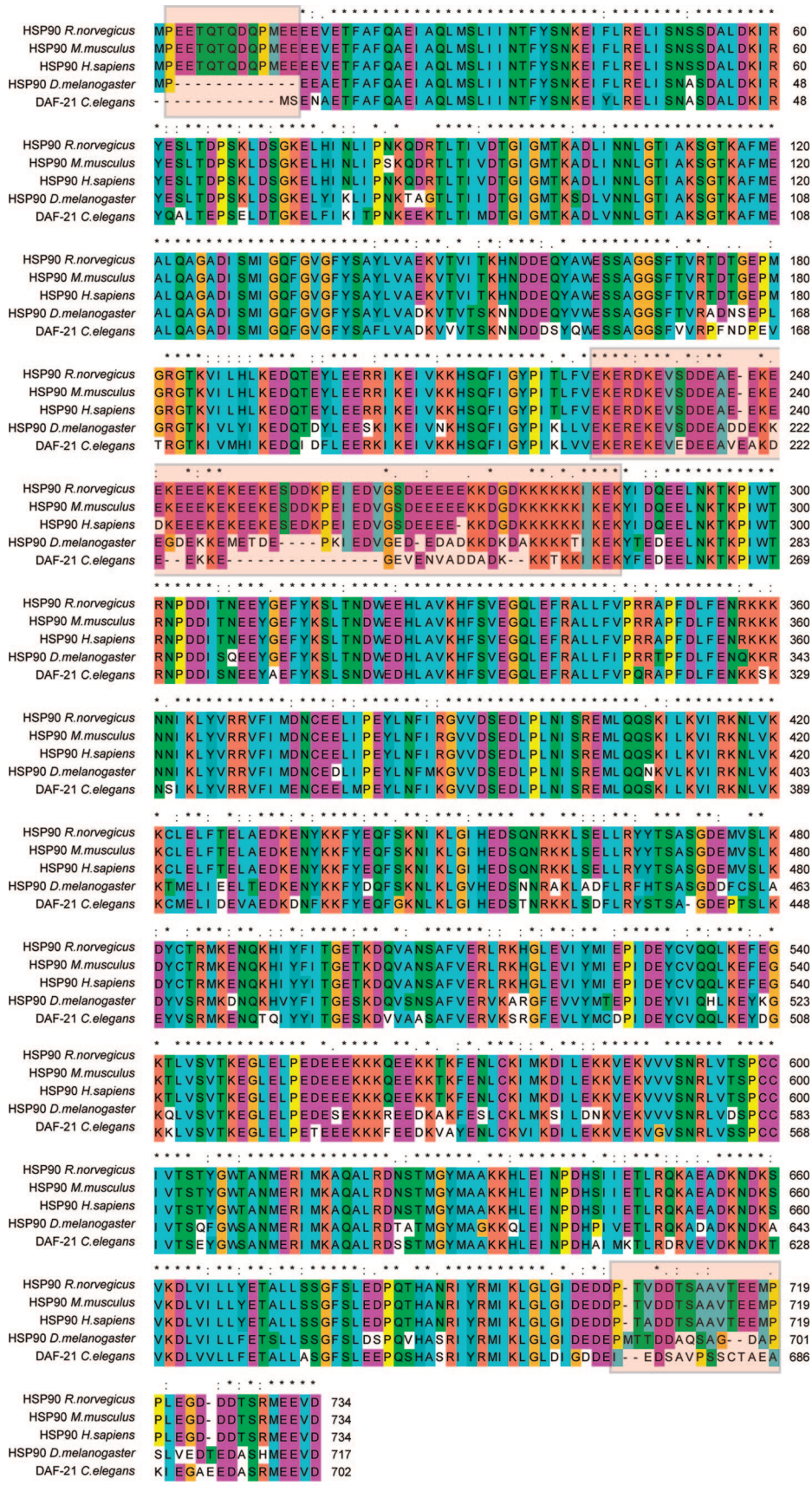


**Figure 10.** Multiple alignment of conserved HSP90 domains from human (*H. sapiens*), rat (*R. norvegicus*), mouse (*M. musculus*), fly (*D. melanogaster*), and worm (*C. elegans*) species. HSP90 (Heat-Shock Protein of 90 kDa) is almost identical from worms to human with a sequence similarity of over 95% except in the central region of the protein, where vertebrate HSP90 display a longer sequence of charged residues and short N- and C-terminal domains (red boxes). All protein multiple alignments were generated using the ClustalX interface, running ClustalW software. Protein residues are colored according to their biochemical properties and their conservation across the alignment. Each position is additionally labeled according to its conservation level (* highly conserved residue, : conserved residue type or conserved residue in most sequences,. less conserved residue type, no conservation).

protein aggregation, oxidative stress, and age, three core components of neurodegeneration that are inherent to multiple neuropathologies.

#### 3.2.4. Chaperones and PD Genes

DJ-1 colocolizes with HSP70, CHIP, and mtHSP70[322] (Figure 1B). Oxidative stress leads to translocation of wt DJ-1 to the mitochondria and enhances its association with mtHSP70. Compared to wt DJ-1, the L166P mutant binds with greater affinity to HSP70 and CHIP but fails to translocate to the mitochondria under conditions of oxidative stress.[322,451,452] As stressed previously, LRRK2 may interact with chaperones such as HSP90, the heat shock cognate of 71 kDa, the stress-70 protein mitochondrial precursor, and midasin.[390] According to its localization in Lewy Bodies,[376] it may also colocalize and/or interact with HSP70. Recent results demonstrated that CHIP can bind, ubiquitinate, and promote proteosomal degradation of LRRK2.[453] On the other hand, HSP90 chaperone binding protects LRRK2 from degradation and favors LRRK2 kinase-dependent toxicity.[453−455] Whether PINK1 colocolizes with HSP70, CHIP, and mtHSP70 has yet to be determined. However, loss of interaction between PINK1 and HSP90 due to PINK1 L347P substitution or HSP90 inhibitors induced a decrease in PINK1 levels and the neuroprotective effect, suggesting that HSP90 is required for the prevention of PINK1 degradation.[288] HSP90 is a key chaperone in the genetic network of PD, as it interacts physically with at least 4 PD genes: PARK2/Parkin, PARK5/UCH-L1, PARK6/PINK1, and PARK8/LRRK2/Dardarin.

### 3.3. Mn and PD Associated Genes: Recent Insights

Mn involvement in PD was suspected decades ago. However, the first mechanistic insights came from studies published in the last five years, which provide evidence of interaction between Mn toxicity and FPD genes. In 2004, it was shown that Mn treatment increases α-synuclein toxicity synergistically with α-synuclein overexpression in neuroblastoma cells expressing the DA transporter (DAT), whereas DA, MPP+, and iron did not.[128] It was also shown that Parkin protects against Mn-induced cell death, specifically in DA expressing cells and not in non-DAergic neurons. Moreover, Mn treatment led to the up-regulation of the ER-stress factors including Parkin, and Parkin redistributed to perinuclear Golgi in two distinct DAergic cell lines but not in non-DAergic neurons.[127] This last study also unraveled a genetic interaction between Park9/Atp13a2 and α-synuclein, and it found that Atp13a2 partially protected cells against Mn toxicity.[211] Those studies bring to bear direct arguments suggesting that Mn can take part in the etiology of PD by adversely affecting FPD associated proteins, which naturally protect DAergic neurons against oxidative damage (see above).

### 3.4. Future Directions

#### 3.4.1. Questions To Be Addressed

Remarkable progress has been accomplished over the last few decades in understanding cellular mechanisms involved in PD and Mn-induced neurotoxicity, largely reflecting upon the identification of the α-synuclein gene and the aggregation properties of its protein product. The involvement of oxidative stress, cell death mechanisms, and mitochondrial metabolism suspected in many other neurodegenerative diseases have further contributed to a complex picture of PD-related diseases and their presentation at the cellular level. However, it is very unclear to which extent the various sources of oxidative stress (mitochondrial activity or demise, exogenous compounds such as Mn, genetic variations in antioxidant genes), the degradation pathways (endolysosomal and ubiquitin-proteosomal pathways), the genotoxicity vs proteotoxicity or lipid peroxidation, and the development of inclusions contribute to the penultimate neurotoxicity and by inference the clinical syndrome. Furthermore, the sequence of the cellular events leading to the neurodegeneration is not well understood. It likely reflects upon the difficulty in developing well-adjusted end efficient therapeutic strategies against PD and similar disorders. In addition to identifying more genetic factors that will help link molecularly the cellular pathways contributing to manganism and PD, quantitative multifactorial approaches that integrate genetic variability and environmental factors will be required.

#### 3.4.2. Need for New Approaches

Human genetics studies have been highly instrumental in identifying single genes that are responsible for early onset FPD. The identification of PARK genes led to the formulation and testing of hypotheses on the molecular basis of FPD. However, this approach, which can occasionally lead to false positives, is extremely time-consuming and limited by the access to human populations that are genetically related and display similar Parkinsonian symptoms. When dealing with manganism, the symptoms are versatile; exposure levels are not necessarily comparable, depending upon the Mn species involved and their pharmacokinetics, which themselves are confounded by factors, such as individual weight, sex, age at exposure, etc. Moreover, diet control, regular assessment of various physiological parameters, and access to organ tissues of interest is limited. Within this context, identifying contributing genetic factors to the disease may be very tedious and not the optimal approach.

The use of experimental animal models offers the advantages of a well controlled system, in terms of both environmental and genetic determinants, and provides access to organs at various stages of the development of the disease, to the extent allowed by ethics in animal experimentation. Simian and rodent models have significantly contributed to our knowledge on Mn-induced brain injury, Mn transport and deposition, as well as Mn-induced transcriptional changes in neurons, astrocytes, and microglia. A few studies also addressed the synergistic effects between Mn and DAergic neurodegeneration-inducing drugs.[81,126,456−458] Nevertheless, very few transgenic and knockout rodent models are currently available, restricting genetic analysis of Mn toxicity.

Smaller organisms such as the zebra fish, the fruit fly, *C. elegans*, or baker's yeast make available a high genetic diversity and a large panel of molecular biology and high-throughput techniques to investigate gene−gene and gene−toxicant interactions, provided the molecular pathways of interest are conserved. Analysis of the PD-linked protein sequences, as shown in our multiple alignments, reveals a strong conservation within the animal kingdom and down to the yeast. Recent work conducted in yeast and in *C. elegans* unraveled conserved genetic networks, molecular pathways, and new candidate genes that may be involved in PD.[192,201,210,219,223,224,416]

Overall, except α-synuclein, all the major proteins whose mutations lead to PD are strongly conserved in *C. elegans*, especially at the level of their functional domains. Importantly, most of the missense mutations involved in PD target highly conserved residues and could be studied in *C. elegans*. In addition, the only missing partner (α-synuclein) can be transvected to the worm and can lead to protein inclusions similar to the Lewy Bodies. *C. elegans* is the simplest, least expensive, fastest growing, most amenable, and best described (developmentally and genetically) *in vivo* model available, notably for toxicology studies.[228] Our recent work (unpublished data) further shows that Mn physiology in the worm shows striking similarities, in terms of Mn transport and neurotoxicity to mammalian species. Therefore, we expect *C. elegans* to become a model of choice to decipher the genetic network implicated in PD-related disorders and to investigate gene-environment interactions in manganism.

## 4. Conclusions

The systematic observation of the essential properties of Mn as a cofactor for enzymes with antioxidant activity (SOD2, catalase, glutamine synthetase) and toxic properties as an oxidant is reminiscent of the way other essential heavy metals, such as copper, trigger neurodegeneration.[459] Overall, Mn likely plays a role in many neurodegenerative disorders (PD, ALS, AD, and Ataxia), all of which rely on similar intracellular mechanisms involving oxidative stress, mitochondrial impairment, and protein aggregation. The most striking case-study example of this pleiotropic effect of Mn may have been found in Northern Australia at Angurugu.[460] The "Angurugu" syndrome starts from early childhood to adulthood and includes symptoms related to manganism, PD, AD, ataxia, and ALS. This broad range of symptoms that can appear very early in development and their severity are believed to be due to extreme ecological conditions of calcium and iron depletion and high Mn.[460] However, the singularity of the Mn-induced Parkinsonism, or manganism, and its resemblance to PD strongly support a specific role of Mn rather than any other metal in PD, and it differs from the way Mn could contribute to other neurological disorders.

Though manganism and PD patients are distinguishable by careful MRI[461] or PET scan analysis and display distinct sequences of neurological symptoms during early phases of the disease, both syndromes share striking similarities at the clinical, physiological, cellular, and molecular levels, relying on common neurodegenerative pathways. Because airborne manganese is present in both urban (industrial activities, gas additives) and rural environments (pesticides) and easily absorbed via the olfactory tract, occupational and environmental exposures to Mn represent a significant public concern. Among metals involved in neurodegenerative disorders, Mn specifically accumulates in the brain regions and the neurons primarily affected in PD. This specific accumulation is likely related to the higher expression levels of the Mn-transporter DMT1 in those regions. DMT1 is also a main transporter of iron, whose physiology is perturbed in both PD and Mn-intoxicated patients. Metal cations in general and $Mn^{2+}$ and $Mn^{3+}$ in particular are able to react with biogenic amines (such as dopamine) through the Fenton's reaction and produce ROS, which would further lead to oxidative stress-driven dopaminergic neurodegeneration, similarly to what is observed in PD. Mn toxicity also involves protein aggregation, energy depletion, and mitochondrial impairment, which represent other hallmarks of PD. Moreover, PARK genes responsible for FPD draw a genetic network that intersects with Mn-toxicity targets.

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## 6. References

(1) Post, J. E. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 3447–54.
(2) Saric, M. In *Handbook on The Toxicology of Metals*; Friberg, L. N. G. F., Vouk, V. B., Ed.; Elsevier Science Publishers B.V.: Amsterdam, 1986; Vol. II.
(3) Wedler, F. C.; Denman, R. B. *Curr. Top. Cell Regul.* **1984**, *24*, 153–69.
(4) Addess, K. J.; Basilion, J. P.; Klausner, R. D.; Rouault, T. A.; Pardi, A. *J. Mol. Biol.* **1997**, *274*, 72–83.
(5) Aschner, M.; Gannon, M.; Kimelberg, H. K. *J. Neurochem.* **1992**, *58*, 730–5.
(6) Fitsanakis, V. A.; Aschner, M. *Toxicol. Appl. Pharmacol.* **2005**, *204*, 343–54.
(7) Liao, S. L.; Chen, C. J. *Neuroreport* **2001**, *12*, 3877–81.
(8) Malecki, E. A.; Devenyi, A. G.; Beard, J. L.; Connor, J. R. *J. Neurosci. Res.* **1999**, *56*, 113–22.
(9) Prohaska, J. R. *Physiol. Rev.* **1987**, *67*, 858–901.
(10) Takeda, A.; Sotogaku, N.; Oku, N. *Brain Res.* **2003**, *965*, 279–82.
(11) Aschner, M. *Environ. Health Perspect.* **2000**, *108* (3), 429–32.
(12) Aschner, M. *Neurotoxicology* **2002**, *23*, 123–5.
(13) Morgan, J. M. *Cancer* **1972**, *29*, 710–3.
(14) Roels, H.; Lauwerys, R.; Buchet, J. P.; Genet, P.; Sarhan, M. J.; Hanotiau, I.; de Fays, M.; Bernard, A.; Stanescu, D. *Am. J. Ind. Med.* **1987**, *11*, 307–27.
(15) Nemery, B. *Eur. Respir. J.* **1990**, *3*, 202–19.
(16) Antonini, J. M.; Taylor, M. D.; Zimmer, A. T.; Roberts, J. R. *J. Toxicol. Environ. Health A* **2004**, *67*, 233–49.
(17) Dorman, D. C.; Struve, M. F.; Gross, E. A.; Wong, B. A.; Howroyd, P. C. *Respir. Res.* **2005**, *6*, 121.
(18) Bowler, R. M.; Roels, H. A.; Nakagawa, S.; Drezgic, M.; Diamond, E.; Park, R.; Koller, W.; Bowler, R. P.; Mergler, D.; Bouchard, M.; Smith, D.; Gwiazda, R.; Doty, R. L. *Occup. Environ. Med.* **2007**, *64*, 167–77.
(19) Boojar, M. M.; Goodarzi, F. *J. Occup. Environ. Med.* **2002**, *44*, 282–90.
(20) Dorman, D. C.; McManus, B. E.; Parkinson, C. U.; Manuel, C. A.; McElveen, A. M.; Everitt, J. I. *Inhal. Toxicol.* **2004**, *16*, 481–8.
(21) Yamada, M.; Ohno, S.; Okayasu, I.; Okeda, R.; Hatakeyama, S.; Watanabe, H.; Ushio, K.; Tsukagoshi, H. *Acta Neuropathol.* **1986**, *70*, 273–8.
(22) Baranski, B. *Environ. Health Perspect.* **1993**, *101* (2), 81–90.
(23) Cama, E.; Colleluori, D. M.; Emig, F. A.; Shin, H.; Kim, S. W.; Kim, N. N.; Traish, A. M.; Ash, D. E.; Christianson, D. W. *Biochemistry* **2003**, *42*, 8445–51.
(24) Dorman, D. C.; Struve, M. F.; James, R. A.; McManus, B. E.; Marshall, M. W.; Wong, B. A. *Toxicol. Sci.* **2001**, *60*, 242–51.
(25) Dorman, D. C.; Struve, M. F.; Wong, B. A. *Neurotoxicology* **2002**, *23*, 185–95.
(26) Aschner, M.; Aschner, J. L. *Neurosci. Biobehav. Rev.* **1991**, *15*, 333–40.
(27) Saric, M. *Am. J. Ind. Med.* **1986**, *9*, 217–9.
(28) Thompson, K.; Molina, R. M.; Donaghey, T.; Schwob, J. E.; Brain, J. D.; Wessling-Resnick, M. *FASEB J.* **2007**, *21*, 223–30.
(29) Calne, D. B.; Chu, N. S.; Huang, C. C.; Lu, C. S.; Olanow, W. *Neurology* **1994**, *44*, 1583–6.
(30) Cersosimo, M. G.; Koller, W. C. *Neurotoxicology* **2006**, *27*, 340–6.
(31) Olanow, C. W. *Ann. N.Y. Acad. Sci.* **2004**, *1012*, 209–23.
(32) Pfeifer, G. D.; Roper, J. M.; Dorman, D.; Lynam, D. R. *Sci. Total Environ.* **2004**, *334−335*, 397–408.
(33) Ressler, T.; Wong, J.; Roos, J. *J. Synchrotron Radiat.* **1999**, *6*, 656–8.
(34) Rollin, H.; Mathee, A.; Levin, J.; Theodorou, P.; Wewers, F. *Environ. Res.* **2005**, *97*, 93–9.
(35) Sly, L. I.; Hodgkinson, M. C.; Arunpairojana, V. *Appl. Environ. Microbiol.* **1990**, *56*, 628–39.
(36) Bushnell, D. M.; Martin, M. L. *Qual. Life Res.* **1999**, *8*, 345–50.
(37) Dorsey, E. R.; Constantinescu, R.; Thompson, J. P.; Biglan, K. M.; Holloway, R. G.; Kieburtz, K.; Marshall, F. J.; Ravina, B. M.; Schifitto, G.; Siderowf, A.; Tanner, C. M. *Neurology* **2007**, *68*, 384–6.

(38) Wilson, J. M.; Levey, A. I.; Rajput, A.; Ang, L.; Guttman, M.; Shannak, K.; Niznik, H. B.; Hornykiewicz, O.; Pifl, C.; Kish, S. J. *Neurology* **1996**, *47*, 718–26.
(39) Dauer, W.; Przedborski, S. *Neuron* **2003**, *39*, 889–909.
(40) Samii, A.; Nutt, J. G.; Ransom, B. R. *Lancet* **2004**, *363*, 1783–93.
(41) Wood-Kaczmar, A.; Gandhi, S.; Wood, N. W. *Trends Mol. Med.* **2006**, *12*, 521–8.
(42) Finkelstein, M. M.; Jerrett, M. *Environ. Res.* **2007**, *104*, 420–32.
(43) Klockgether, T.; Turski, L. *Trends Neurosci.* **1989**, *12*, 285–6.
(44) Newland, M. C.; Ceckler, T. L.; Kordower, J. H.; Weiss, B. *Exp. Neurol.* **1989**, *106*, 251–8.
(45) Suzuki, N.; Nakamura, Y.; Kobayashi, N.; Sato, T. *Tohoku J. Exp. Med.* **1975**, *116*, 233–40.
(46) Rose, C.; Butterworth, R. F.; Zayed, J.; Normandin, L.; Todd, K.; Michalak, A.; Spahr, L.; Huet, P. M.; Pomier-Layrargues, G. *Gastroenterology* **1999**, *117*, 640–4.
(47) Ikeda, S.; Yamaguchi, Y.; Sera, Y.; Ohshiro, H.; Uchino, S.; Yamashita, Y.; Ogawa, M. *Transplantation* **2000**, *69*, 2339–43.
(48) Iwase, K.; Higaki, J.; Mikata, S.; Tanaka, Y.; Kondoh, H.; Yoshikawa, M.; Hori, S.; Kamiike, W. *Dig Surg.* **2002**, *19*, 174–83.
(49) da Silva, C. J.; da Rocha, A. J.; Mendes, M. F.; Braga, A. P.; Jeronymo, S. *Arch. Neurol.* **2008**, *65*, 983.
(50) Burdo, J. R.; Menzies, S. L.; Simpson, I. A.; Garrick, L. M.; Garrick, M. D.; Dolan, K. G.; Haile, D. J.; Beard, J. L.; Connor, J. R. *J. Neurosci. Res.* **2001**, *66*, 1198–207.
(51) Huang, E.; Ong, W. Y.; Connor, J. R. *Neuroscience* **2004**, *128*, 487–96.
(52) Williams, K.; Wilson, M. A.; Bressler, J. *Cell Mol. Biol. (Noisy-le-grand)* **2000**, *46*, 563–71.
(53) Au, C.; Benedetto, A.; Aschner, M. *Neurotoxicology* **2008**, *29*, 569–76.
(54) Knopfel, M.; Zhao, L.; Garrick, M. D. *Biochemistry* **2005**, *44*, 3454–65.
(55) Roth, J. A.; Garrick, M. D. *Biochem. Pharmacol.* **2003**, *66*, 1–13.
(56) Schulz, J. B.; Falkenburger, B. H. *Cell Tissue Res.* **2004**, *318*, 135–47.
(57) Olanow, C. W.; Tatton, W. G. *Annu. Rev. Neurosci.* **1999**, *22*, 123–44.
(58) Kim, Y.; Kim, J. M.; Kim, J. W.; Yoo, C. I.; Lee, C. R.; Lee, J. H.; Kim, H. K.; Yang, S. O.; Chung, H. K.; Lee, D. S.; Jeon, B. *Mov. Disord.* **2002**, *17*, 568–75.
(59) Butterworth, R. F.; Spahr, L.; Fontaine, S.; Layrargues, G. P. *Metab. Brain Dis.* **1995**, *10*, 259–67.
(60) Chen, M. K.; Lee, J. S.; McGlothan, J. L.; Furukawa, E.; Adams, R. J.; Alexander, M.; Wong, D. F.; Guilarte, T. R. *Neurotoxicology* **2006**, *27*, 229–36.
(61) Guilarte, T. R.; Chen, M. K.; McGlothan, J. L.; Verina, T.; Wong, D. F.; Zhou, Y.; Alexander, M.; Rohde, C. A.; Syversen, T.; Decamp, E.; Koser, A. J.; Fritz, S.; Gonczi, H.; Anderson, D. W.; Schneider, J. S. *Exp. Neurol.* **2006**, *202*, 381–90.
(62) Donaldson, J.; LaBella, F. S.; Gesser, D. *Neurotoxicology* **1981**, *2*, 53–64.
(63) Gianutsos, G.; Murray, M. T. *Neurotoxicology* **1982**, *3*, 75–81.
(64) Leung, T. K.; Lai, J. C.; Tricklebank, M.; Davison, A. N.; Lim, L. *J. Neurochem.* **1982**, *39*, 1496–9.
(65) Lista, A.; Abarca, J.; Ramos, C.; Daniels, A. J. *Life Sci.* **1986**, *38*, 2121–7.
(66) Parenti, M.; Rusconi, L.; Cappabianca, V.; Parati, E. A.; Groppetti, A. *Brain Res.* **1988**, *473*, 236–40.
(67) Lloyd, R. V. *Chem. Res. Toxicol.* **1995**, *8*, 111–6.
(68) Ranasinghe, J. G.; Liu, M. C.; Sakakibara, Y.; Suiko, M. *J. Biochem.* **2000**, *128*, 477–80.
(69) Montes, S.; Alcaraz-Zubeldia, M.; Muriel, P.; Rios, C. *Brain Res.* **2001**, *891*, 123–9.
(70) Tran, T. T.; Chowanadisai, W.; Crinella, F. M.; Chicz-DeMet, A.; Lonnerdal, B. *Neurotoxicology* **2002**, *23*, 635–43.
(71) Vidal, L.; Alfonso, M.; Campos, F.; Faro, L. R.; Cervantes, R. C.; Duran, R. *Neurochem. Res.* **2005**, *30*, 1147–54.
(72) McDougall, S. A.; Reichel, C. M.; Farley, C. M.; Flesher, M. M.; Der-Ghazarian, T.; Cortez, A. M.; Wacan, J. J.; Martinez, C. E.; Varela, F. A.; Butt, A. E.; Crawford, C. A. *Neuroscience* **2008**, *154*, 848–60.
(73) Prabhakaran, K.; Ghosh, D.; Chapman, G. D.; Gunasekar, P. G. *Brain Res. Bull.* **2008**, *76*, 361–7.
(74) Kim, H. Y.; Lee, C. K.; Lee, J. T.; Moon, C. S.; Ha, S. C.; Kang, S. G.; Kim, D. H.; Kim, H. D.; Ahn, J. H.; Lee, S. B.; Kang, M. G. *Neuroreport* **2009**, *20*, 69–73.
(75) Donaldson, J.; McGregor, D.; LaBella, F. *Can. J. Physiol. Pharmacol.* **1982**, *60*, 1398–405.
(76) Shen, X. M.; Dryhurst, G. *Chem. Res. Toxicol.* **1998**, *11*, 824–37.
(77) Ahmadi, F. A.; Grammatopoulos, T. N.; Poczobutt, A. M.; Jones, S. M.; Snell, L. D.; Das, M.; Zawada, W. M. *Neurochem. Res.* **2008**, *33*, 886–901.
(78) Baranyi, M.; Milusheva, E.; Vizi, E. S.; Sperlagh, B. *J. Chromatogr., A* **2006**, *1120*, 13–20.
(79) Graumann, R.; Paris, I.; Martinez-Alvarado, P.; Rumanque, P.; Perez-Pastene, C.; Cardenas, S. P.; Marin, P.; Diaz-Grez, F.; Caviedes, R.; Caviedes, P.; Segura-Aguilar, J. *Pol. J. Pharmacol.* **2002**, *54*, 573–9.
(80) Florence, T. M.; Stauber, J. L. *Sci. Total Environ.* **1989**, *78*, 233–40.
(81) Oikawa, S.; Hirosawa, I.; Tada-Oikawa, S.; Furukawa, A.; Nishiura, K.; Kawanishi, S. *Free Radical Biol. Med.* **2006**, *41*, 748–56.
(82) Fei, Q.; McCormack, A. L.; Di Monte, D. A.; Ethell, D. W. *J. Biol. Chem.* **2008**, *283*, 3357–64.
(83) Lee, S. Y.; Moon, Y.; Hee Choi, D.; Jin Choi, H.; Hwang, O. *Neurobiol. Dis.* **2007**, *25*, 112–20.
(84) Milusheva, E.; Baranyi, M.; Kittel, A.; Sperlagh, B.; Vizi, E. S. *Free Radical Biol. Med.* **2005**, *39*, 133–42.
(85) Park, S. U.; Ferrer, J. V.; Javitch, J. A.; Kuhn, D. M. *J. Neurosci.* **2002**, *22*, 4399–405.
(86) Lewers, J. C.; Ceballos-Picot, I.; Shirley, T. L.; Mockel, L.; Egami, K.; Jinnah, H. A. *Neuroscience* **2008**, *152*, 761–72.
(87) Vernier, P.; Moret, F.; Callier, S.; Snapyan, M.; Wersinger, C.; Sidhu, A. *Ann. N.Y. Acad. Sci.* **2004**, *1035*, 231–49.
(88) Colton, C. A.; Pagan, F.; Snell, J.; Colton, J. S.; Cummins, A.; Gilbert, D. L. *Exp. Neurol.* **1995**, *132*, 54–61.
(89) Han, S. K.; Mytilineou, C.; Cohen, G. *J. Neurochem.* **1996**, *66*, 501–10.
(90) Ebadi, M.; Ramana Kumari, M. V.; Hiramatsu, M.; Hao, R.; Pfeiffer, R. F.; Rojas, P. *Restor. Neurol. Neurosci.* **1998**, *12*, 103–11.
(91) Mytilineou, C.; Leonardi, E. K.; Radcliffe, P.; Heinonen, E. H.; Han, S. K.; Werner, P.; Cohen, G.; Olanow, C. W. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 700–6.
(92) Chiueh, C. C.; Andoh, T.; Lai, A. R.; Lai, E.; Krishna, G. *Neurotox. Res.* **2000**, *2*, 293–310.
(93) Wu, R. M.; Chen, R. C.; Chiueh, C. C. *Ann. N.Y. Acad. Sci.* **2000**, *899*, 255–61.
(94) Ibi, M.; Sawada, H.; Nakanishi, M.; Kume, T.; Katsuki, H.; Kaneko, S.; Shimohama, S.; Akaike, A. *Neuropharmacology* **2001**, *40*, 761–71.
(95) Nakamura, K.; Bindokas, V. P.; Kowlessur, D.; Elas, M.; Milstien, S.; Marks, J. D.; Halpern, H. J.; Kang, U. J. *J. Biol. Chem.* **2001**, *276*, 34402–7.
(96) Mohanakumar, K. P.; Thomas, B.; Sharma, S. M.; Muralikrishnan, D.; Chowdhury, R.; Chiueh, C. C. *Ann. N.Y. Acad. Sci.* **2002**, *962*, 389–401.
(97) Madsen, J. T.; Jansen, P.; Hesslinger, C.; Meyer, M.; Zimmer, J.; Gramsbergen, J. B. *J. Neurochem.* **2003**, *85*, 214–23.
(98) Zbarsky, V.; Datla, K. P.; Parkar, S.; Rai, D. K.; Aruoma, O. I.; Dexter, D. T. *Free Radical Res.* **2005**, *39*, 1119–25.
(99) Han, J. M.; Lee, Y. J.; Lee, S. Y.; Kim, E. M.; Moon, Y.; Kim, H. W.; Hwang, O. *J Pharmacol. Exp. Ther.* **2007**, *321*, 249–56.
(100) Jakel, R. J.; Townsend, J. A.; Kraft, A. D.; Johnson, J. A. *Brain Res.* **2007**, *1144*, 192–201.
(101) Hwang, Y. P.; Jeong, H. G. *FEBS Lett.* **2008**, *582*, 2655–62.
(102) Jin, F.; Wu, Q.; Lu, Y. F.; Gong, Q. H.; Shi, J. S. *Eur. J. Pharmacol.* **2008**, *600*, 78–82.
(103) Siebert, A.; Desai, V.; Chandrasekaran, K.; Fiskum, G.; Jafri, M. S. J. Neurosci. Res., in press.
(104) Chiueh, C. C.; Wu, R. M.; Mohanakumar, K. P.; Sternberger, L. M.; Krishna, G.; Obata, T.; Murphy, D. L. *Ann. N.Y. Acad. Sci.* **1994**, *738*, 25–36.
(105) De Iuliis, A.; Grigoletto, J.; Recchia, A.; Giusti, P.; Arslan, P. *Clin. Chim. Acta* **2005**, *357*, 202–9.
(106) Perier, C.; Tieu, K.; Guegan, C.; Caspersen, C.; Jackson-Lewis, V.; Carelli, V.; Martinuzzi, A.; Hirano, M.; Przedborski, S.; Vila, M. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 19126–31.
(107) Sherer, T. B.; Betarbet, R.; Kim, J. H.; Greenamyre, J. T. *Neurosci. Lett.* **2003**, *341*, 87–90.
(108) Jenner, P. *Mov. Disord.* **1998**, *13* (1), 24–34.
(109) Wang, H.; Shimoji, M.; Yu, S. W.; Dawson, T. M.; Dawson, V. L. *Ann. N.Y. Acad. Sci.* **2003**, *991*, 132–9.
(110) Mattson, M. P. *Neuromol. Med.* **2003**, *3*, 65–94.
(111) Golembiowska, K.; Konieczny, J.; Ossowska, K.; Wolfarth, S. *Amino Acids* **2002**, *23*, 199–205.
(112) Greenamyre, J. T.; MacKenzie, G.; Peng, T. I.; Stephans, S. E. *Biochem. Soc. Symp.* **1999**, *66*, 85–97.
(113) Beal, M. F. *Ann. Neurol.* **1995**, *38*, 357–66.
(114) Mela, L. *Arch. Biochem. Biophys.* **1968**, *123*, 286–93.
(115) Gunter, R. E.; Puskin, J. S.; Russell, P. R. *Biophys. J.* **1975**, *15*, 319–33.
(116) Liccione, J.; Azzaro, A. J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 151–8.
(117) Gavin, C. E.; Gunter, K. K.; Gunter, T. E. *Neurotoxicology* **1999**, *20*, 445–53.

(118) Brouillet, E. P.; Shinobu, L.; McGarvey, U.; Hochberg, F.; Beal, M. F. *Exp. Neurol.* **1993**, *120*, 89–94.
(119) Oestreicher, E.; Sengstock, G. J.; Riederer, P.; Olanow, C. W.; Dunn, A. J.; Arendash, G. W. *Brain Res.* **1994**, *660*, 8–18.
(120) Kienzl, E.; Puchinger, L.; Jellinger, K.; Linert, W.; Stachelberger, H.; Jameson, R. F. *J. Neurol. Sci.* **1995**, *134*, 69–78.
(121) Montgomery, J.; Ste-Marie, L.; Boismenu, D.; Vachon, L. *Free Radical Biol. Med.* **1995**, *19*, 927–33.
(122) Loschmann, P. A.; Lange, K. W.; Wachtel, H.; Turski, L. *J. Neural Transm.* **1994**, *43*, 133–43.
(123) Takeda, A. *Brain Res. Brain Res. Rev.* **2003**, *41*, 79–87.
(124) Chun, H. S.; Gibson, G. E.; DeGiorgio, L. A.; Zhang, H.; Kidd, V. J.; Son, J. H. *J. Neurochem.* **2001**, *76*, 1010–21.
(125) Tomas-Camardiel, M.; Herrera, A. J.; Venero, J. L.; Cruz Sanchez-Hidalgo, M.; Cano, J.; Machado, A. *Brain Res. Mol. Brain Res.* **2002**, *103*, 116–29.
(126) Migheli, R.; Godani, C.; Sciola, L.; Delogu, M. R.; Serra, P. A.; Zangani, D.; De Natale, G.; Miele, E.; Desole, M. S. *J. Neurochem.* **1999**, *73*, 1155–63.
(127) Higashi, Y.; Asanuma, M.; Miyazaki, I.; Hattori, N.; Mizuno, Y.; Ogawa, N. *J. Neurochem.* **2004**, *89*, 1490–7.
(128) Pifl, C.; Khorchide, M.; Kattinger, A.; Reither, H.; Hardy, J.; Hornykiewicz, O. *Neurosci. Lett.* **2004**, *354*, 34–7.
(129) Hirata, Y. *Neurotoxicol. Teratol.* **2002**, *24*, 639–53.
(130) HaMai, D.; Bondy, S. C. *Ann. N.Y. Acad. Sci.* **2004**, *1012*, 129–41.
(131) Stredrick, D. L.; Stokes, A. H.; Worst, T. J.; Freeman, W. M.; Johnson, E. A.; Lash, L. H.; Aschner, M.; Vrana, K. E. *Neurotoxicology* **2004**, *25*, 543–53.
(132) Song, W.; Su, H.; Song, S.; Paudel, H. K.; Schipper, H. M. *J. Cell Physiol.* **2006**, *206*, 655–63.
(133) Reaney, S. H.; Kwik-Uribe, C. L.; Smith, D. R. *Chem. Res. Toxicol.* **2002**, *15*, 1119–26.
(134) Reaney, S. H.; Smith, D. R. *Toxicol. Appl. Pharmacol.* **2005**, *205*, 271–81.
(135) Hsu, L. J.; Sagara, Y.; Arroyo, A.; Rockenstein, E.; Sisk, A.; Mallory, M.; Wong, J.; Takenouchi, T.; Hashimoto, M.; Masliah, E. *Am. J. Pathol.* **2000**, *157*, 401–10.
(136) Tanaka, Y.; Engelender, S.; Igarashi, S.; Rao, R. K.; Wanner, T.; Tanzi, R. E.; Sawa, A. B. L. D.; Dawson, T. M.; Ross, C. A. *Hum. Mol. Genet.* **2001**, *10*, 919–26.
(137) Sherer, T. B.; Betarbet, R.; Stout, A. K.; Lund, S.; Baptista, M.; Panov, A. V.; Cookson, M. R.; Greenamyre, J. T. *J. Neurosci.* **2002**, *22*, 7006–15.
(138) Sherer, T. B.; Betarbet, R.; Testa, C. M.; Seo, B. B.; Richardson, J. R.; Kim, J. H.; Miller, G. W.; Yagi, T.; Matsuno-Yagi, A.; Greenamyre, J. T. *J. Neurosci.* **2003**, *23*, 10756–64.
(139) Witholt, R.; Gwiazda, R. H.; Smith, D. R. *Neurotoxicol. Teratol.* **2000**, *22*, 851–61.
(140) Jellinger, K. A. *J. Neural Transm.* **2000**, *107*, 1–29.
(141) Blum, D.; Torch, S.; Lambeng, N.; Nissou, M.; Benabid, A. L.; Sadoul, R.; Verna, J. M. *Prog. Neurobiol.* **2001**, *65*, 135–72.
(142) Kosel, S.; Hofhaus, G.; Maassen, A.; Vieregge, P.; Graeber, M. B. *Biol. Chem.* **1999**, *380*, 865–70.
(143) Lotharius, J.; Dugan, L. L.; O'Malley, K. L. *J. Neurosci.* **1999**, *19*, 1284–93.
(144) Choi, W. S.; Yoon, S. Y.; Oh, T. H.; Choi, E. J.; O'Malley, K. L.; Oh, Y. J. *J. Neurosci. Res.* **1999**, *57*, 86–94.
(145) Aoki, E.; Yano, R.; Yokoyama, H.; Kato, H.; Araki, T. *Exp. Mol. Pathol.* **2009**, *86*, 57–64.
(146) Anantharam, V.; Kaul, S.; Song, C.; Kanthasamy, A.; Kanthasamy, A. G. *Neurotoxicology* **2007**, *28*, 988–97.
(147) Kaul, S.; Kanthasamy, A.; Kitazawa, M.; Anantharam, V.; Kanthasamy, A. G. *Eur. J. Neurosci.* **2003**, *18*, 1387–401.
(148) Armstrong, J. S.; Hornung, B.; Lecane, P.; Jones, D. P.; Knox, S. J. *Biochem. Biophys. Res. Commun.* **2001**, *289*, 973–8.
(149) Shimizu, S.; Eguchi, Y.; Kamiike, W.; Waguri, S.; Uchiyama, Y.; Matsuda, H.; Tsujimoto, Y. *Oncogene* **1996**, *12*, 2045–50.
(150) Kakinuma, Y.; Miyauchi, T.; Yuki, K.; Murakoshi, N.; Goto, K.; Yamaguchi, I. *J. Cardiovasc. Pharmacol.* **2000**, *36*, S201−4.
(151) Desole, M. S.; Sciola, L.; Delogu, M. R.; Sircana, S.; Migheli, R. *Neurosci. Lett.* **1996**, *209*, 193–6.
(152) Schrantz, N.; Blanchard, D. A.; Mitenne, F.; Auffredou, M. T.; Vazquez, A.; Leca, G. *Cell Death Differ.* **1999**, *6*, 445–53.
(153) Anantharam, V.; Kitazawa, M.; Latchoumycandane, C.; Kanthasamy, A.; Kanthasamy, A. G. *Ann. N.Y. Acad. Sci.* **2004**, *1035*, 271–89.
(154) Hanrott, K.; Gudmunsen, L.; O'Neill, M. J.; Wonnacott, S. *J. Biol. Chem.* **2006**, *281*, 5373–82.
(155) Anantharam, V.; Kitazawa, M.; Wagner, J.; Kaul, S.; Kanthasamy, A. G. *J. Neurosci.* **2002**, *22*, 1738–51.
(156) Latchoumycandane, C.; Anantharam, V.; Kitazawa, M.; Yang, Y.; Kanthasamy, A.; Kanthasamy, A. G. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 46–55.
(157) Benzi, G.; Moretti, A. *Free Radical Biol. Med.* **1995**, *19*, 77–101.
(158) Seo, A. Y.; Xu, J.; Servais, S.; Hofer, T.; Marzetti, E.; Wohlgemuth, S. E.; Knutson, M. D.; Chung, H. Y.; Leeuwenburgh, C. *Aging Cell* **2008**, *7*, 706–16.
(159) Atamna, H. *Ageing Res. Rev.* **2004**, *3*, 303–18.
(160) Choksi, K. B.; Papaconstantinou, J. *Free Radical Biol. Med.* **2008**, *44*, 1795–805.
(161) Yasuda, K.; Ishii, T.; Suda, H.; Akatsuka, A.; Hartman, P. S.; Goto, S.; Miyazawa, M.; Ishii, N. *Mech. Ageing Dev.* **2006**, *127*, 763–70.
(162) Sasaki, T.; Senda, M.; Kim, S.; Kojima, S.; Kubodera, A. *Nucl. Med. Biol.* **2001**, *28*, 25–31.
(163) Sasaki, T.; Unno, K.; Tahara, S.; Shimada, A.; Chiba, Y.; Hoshino, M.; Kaneko, T. *Aging Cell* **2008**, *7*, 459–69.
(164) Parihar, M. S.; Brewer, G. J. *J. Neurosci. Res.* **2007**, *85*, 1018–32.
(165) Williams, W. M.; Chung, Y. W. *Life Sci.* **2006**, *79*, 1638–44.
(166) Yang, W.; Li, J.; Hekimi, S. *Genetics* **2007**, *177*, 2063–74.
(167) Mei, Y.; Gawai, K. R.; Nie, Z.; Ramkumar, V.; Helfert, R. H. *Hear Res.* **1999**, *135*, 169–80.
(168) Andriollo-Sanchez, M.; Hininger-Favier, I.; Meunier, N.; Venneria, E.; O'Connor, J. M.; Maiani, G.; Coudray, C.; Roussel, A. M. *Eur. J. Clin. Nutr.* **2005**, *59* (2), S58−62.
(169) Imam, S. Z.; Karahalil, B.; Hogue, B. A.; Souza-Pinto, N. C.; Bohr, V. A. *Neurobiol. Aging* **2006**, *27*, 1129–36.
(170) Chen, D.; Cao, G.; Hastings, T.; Feng, Y.; Pei, W.; O'Horo, C.; Chen, J. *J. Neurochem.* **2002**, *81*, 1273–84.
(171) Ward, W. F.; Qi, W.; Van Remmen, H.; Zackert, W. E.; Roberts, L. J., 2nd; Richardson, A. *J. Gerontol., A: Biol. Sci. Med. Sci.* **2005**, *60*, 847–51.
(172) Nabeshi, H.; Oikawa, S.; Inoue, S.; Nishino, K.; Kawanishi, S. *Free Radical Res.* **2006**, *40*, 1173–81.
(173) Mutlu-Turkoglu, U.; Ilhan, E.; Oztezcan, S.; Kuru, A.; Aykac-Toker, G.; Uysal, M. *Clin. Biochem.* **2003**, *36*, 397–400.
(174) Levine, R. L. *Free Radical Biol. Med.* **2002**, *32*, 790–6.
(175) Yasuda, K.; Adachi, H.; Fujiwara, Y.; Ishii, N. *J. Gerontol., A: Biol. Sci. Med. Sci.* **1999**, *54*, B47−51. Discussion , B52−3.
(176) Adachi, H.; Fujiwara, Y.; Ishii, N. *J. Gerontol., A: Biol. Sci. Med. Sci.* **1998**, *53*, B240−4.
(177) Ishchenko, A.; Sinitsyna, O.; Krysanova, Z.; Vasyunina, E. A.; Saparbaev, M.; Sidorkina, O.; Nevinsky, G. A. *Med. Sci. Monit.* **2003**, *9*, BR16−24.
(178) Tripathi, S.; Mahdi, A. A.; Nawab, A.; Chander, R.; Hasan, M.; Siddiqui, M. S.; Mahdi, F.; Mitra, K.; Bajpai, V. K. *Brain Res.* **2009**, *1253*, 107–16.
(179) Wills, N. K.; Ramanujam, V. M.; Chang, J.; Kalariya, N.; Lewis, J. R.; Weng, T. X.; van Kuijk, F. J. *Exp. Eye Res.* **2008**, *86*, 41–51.
(180) Erikson, K. M.; Dorman, D. C.; Lash, L. H.; Dobson, A. W.; Aschner, M. *Biol. Trace Elem. Res.* **2004**, *100*, 49–62.
(181) Patel, M.; Li, Q. Y. *Neuroscience* **2003**, *118*, 431–7.
(182) Vanitallie, T. B. *Metab., Clin. Exp.* **2008**, *57* (2), S50−5.
(183) Deng, H.; Le, W.; Guo, Y.; Hunter, C. B.; Xie, W.; Jankovic, J. *Ann. Neurol.* **2005**, *57*, 933–4.
(184) Mellick, G. D.; Siebert, G. A.; Funayama, M.; Buchanan, D. D.; Li, Y.; Imamichi, Y.; Yoshino, H.; Silburn, P. A.; Hattori, N. *Parkinsonism Relat. Disord.* **2009**, *15*, 105–9.
(185) Polymeropoulos, M. H.; Lavedan, C.; Leroy, E.; Ide, S. E.; Dehejia, A.; Dutra, A.; Pike, B.; Root, H.; Rubenstein, J.; Boyer, R.; Stenroos, E. S.; Chandrasekharappa, S.; Athanassiadou, A.; Papapetropoulos, T.; Johnson, W. G.; Lazzarini, A. M.; Duvoisin, R. C.; Di Iorio, G.; Golbe, L. I.; Nussbaum, R. L. *Science* **1997**, *276*, 2045–7.
(186) Kitada, T.; Asakawa, S.; Hattori, N.; Matsumine, H.; Yamamura, Y.; Minoshima, S.; Yokochi, M.; Mizuno, Y.; Shimizu, N. *Nature* **1998**, *392*, 605–8.
(187) Leroy, E.; Boyer, R.; Polymeropoulos, M. H. *DNA Res.* **1998**, *5*, 397–400.
(188) Bonifati, V.; Rizzu, P.; Squitieri, F.; Krieger, E.; Vanacore, N.; van Swieten, J. C.; Brice, A.; van Duijn, C. M.; Oostra, B.; Meco, G.; Heutink, P. *Neurol. Sci.* **2003**, *24*, 159–60.
(189) Le, W. D.; Xu, P.; Jankovic, J.; Jiang, H.; Appel, S. H.; Smith, R. G.; Vassilatis, D. K. *Nat. Genet.* **2003**, *33*, 85–9.
(190) Valente, E. M.; Abou-Sleiman, P. M.; Caputo, V.; Muqit, M. M.; Harvey, K.; Gispert, S.; Ali, Z.; Del Turco, D.; Bentivoglio, A. R.; Healy, D. G.; Albanese, A.; Nussbaum, R.; Gonzalez-Maldonado, R.; Deller, T.; Salvi, S.; Cortelli, P.; Gilks, W. P.; Latchman, D. S.; Harvey, R. J.; Dallapiccola, B.; Auburger, G.; Wood, N. W. *Science* **2004**, *304*, 1158–60.
(191) Paisan-Ruiz, C.; Jain, S.; Evans, E. W.; Gilks, W. P.; Simon, J.; van der Brug, M.; Lopez de Munain, A.; Aparicio, S.; Gil, A. M.; Khan, N.; Johnson, J.; Martinez, J. R.; Nicholl, D.; Carrera, I. M.; Pena, A. S.; de Silva, R.; Lees, A.; Marti-Masso, J. F.; Perez-Tur, J.; Wood, N. W.; Singleton, A. B. *Neuron* **2004**, *44*, 595–600.
(192) Gitler, A. D.; Bevis, B. J.; Shorter, J.; Strathearn, K. E.; Hamamichi, S.; Su, L. J.; Caldwell, K. A.; Caldwell, G. A.; Rochet, J. C.; McCaffery, J. M.; Barlowe, C.; Lindquist, S. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 145–50.

(193) Lotharius, J.; Brundin, P. *Nat. Rev.* **2002**, *3*, 932–42.
(194) Lotharius, J.; Brundin, P. *Hum. Mol. Genet.* **2002**, *11*, 2395–407.
(195) Ben Gedalya, T.; Loeb, V.; Israeli, E.; Altschuler, Y.; Selkoe, D. J.; Sharon, R. *Traffic* **2009**, *10*, 218–34.
(196) Lee, S. J.; Jeon, H.; Kandror, K. V. *Acta Neurobiol. Exp.* **2008**, *68*, 509–15.
(197) Kim, C.; Lee, S. J. *J. Neurochem.* **2008**, *107*, 303–16.
(198) Kahle, P. J.; Neumann, M.; Ozmen, L.; Haass, C. *Ann. N.Y. Acad. Sci.* **2000**, *920*, 33–41.
(199) Narhi, L.; Wood, S. J.; Steavenson, S.; Jiang, Y.; Wu, G. M.; Anafi, D.; Kaufman, S. A.; Martin, F.; Sitney, K.; Denis, P.; Louis, J. C.; Wypych, J.; Biere, A. L.; Citron, M. *J. Biol. Chem.* **1999**, *274*, 9843–6.
(200) Masliah, E.; Rockenstein, E.; Veinbergs, I.; Mallory, M.; Hashimoto, M.; Takeda, A.; Sagara, Y.; Sisk, A.; Mucke, L. *Science* **2000**, *287*, 1265–9.
(201) Kuwahara, T.; Koyama, A.; Gengyo-Ando, K.; Masuda, M.; Kowa, H.; Tsunoda, M.; Mitani, S.; Iwatsubo, T. *J. Biol. Chem.* **2006**, *281*, 334–40.
(202) Forloni, G.; Bertani, I.; Calella, A. M.; Thaler, F.; Invernizzi, R. *Ann. Neurol.* **2000**, *47*, 632–40.
(203) Bennett, J. P., Jr.; Piercey, M. F. *J. Neurol. Sci.* **1999**, *163*, 25–31.
(204) Cullen, V.; Lindfors, M.; Ng, J.; Paetau, A.; Swinton, E.; Kolodziej, P.; Boston, H.; Saftig, P.; Woulfe, J.; Feany, M. B.; Myllykangas, L.; Schlossmacher, M. G.; Tyynela, J. *Mol. Brain* **2009**, *2*, 5.
(205) Qiao, L.; Hamamichi, S.; Caldwell, K. A.; Caldwell, G. A.; Yacoubian, T. A.; Wilson, S.; Xie, Z. L.; Speake, L. D.; Parks, R.; Crabtree, D.; Liang, Q.; Crimmins, S.; Schneider, L.; Uchiyama, Y.; Iwatsubo, T.; Zhou, Y.; Peng, L.; Lu, Y.; Standaert, D. G.; Walls, K. C.; Shacka, J. J.; Roth, K. A.; Zhang, J. *Mol. Brain* **2008**, *1*, 17.
(206) Rideout, H. J.; Lang-Rollin, I.; Stefanis, L. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 2551–62.
(207) Rockenstein, E.; Schwach, G.; Ingolic, E.; Adame, A.; Crews, L.; Mante, M.; Pfragner, R.; Schreiner, E.; Windisch, M.; Masliah, E. *J. Neurosci. Res.* **2005**, *80*, 247–59.
(208) Sevlever, D.; Jiang, P.; Yen, S. H. *Biochemistry* **2008**, *47*, 9678–87.
(209) Wei, J.; Fujita, M.; Nakai, M.; Waragai, M.; Watabe, K.; Akatsu, H.; Rockenstein, E.; Masliah, E.; Hashimoto, M. *J. Biol. Chem.* **2007**, *282*, 28904–14.
(210) Liang, J.; Clark-Dixon, C.; Wang, S.; Flower, T. R.; Williams-Hart, T.; Zweig, R.; Robinson, L. C.; Tatchell, K.; Witt, S. N. *Hum. Mol. Genet.* **2008**, *17*, 3784–95.
(211) Gitler, A. D.; Chesi, A.; Geddie, M. L.; Strathearn, K. E.; Hamamichi, S.; Hill, K. J.; Caldwell, K. A.; Caldwell, G. A.; Cooper, A. A.; Rochet, J. C.; Lindquist, S. *Nat. Genet.* **2009**, *41*, 308–15.
(212) Giasson, B. I.; Duda, J. E.; Murray, I. V.; Chen, Q.; Souza, J. M.; Hurtig, H. I.; Ischiropoulos, H.; Trojanowski, J. Q.; Lee, V. M. *Science* **2000**, *290*, 985–9.
(213) McNaught, K. S.; Jenner, P. *Neurosci. Lett.* **2001**, *297*, 191–4.
(214) Kahle, P. J.; Neumann, M.; Ozmen, L.; Muller, V.; Jacobsen, H.; Schindzielorz, A.; Okochi, M.; Leimer, U.; van Der Putten, H.; Probst, A.; Kremmer, E.; Kretzschmar, H. A.; Haass, C. *J. Neurosci.* **2000**, *20*, 6365–73.
(215) Feany, M. B.; Bender, W. W. *Nature* **2000**, *404*, 394–8.
(216) Feany, M. B. *J. Neuropathol. Exp. Neurol.* **2000**, *59*, 847–56.
(217) Uversky, V. N.; Li, J.; Fink, A. L. *FEBS Lett.* **2001**, *500*, 105–8.
(218) Sauer, H.; Oertel, W. H. *Neuroscience* **1994**, *59*, 401–15.
(219) Ved, R.; Saha, S.; Westlund, B.; Perier, C.; Burnam, L.; Sluder, A.; Hoener, M.; Rodrigues, C. M.; Alfonso, A.; Steer, C.; Liu, L.; Przedborski, S.; Wolozin, B. *J. Biol. Chem.* **2005**, *280*, 42655–68.
(220) Braungart, E.; Gerlach, M.; Riederer, P.; Baumeister, R.; Hoener, M. C. *Neurodegener. Dis.* **2004**, *1*, 175–83.
(221) Vartiainen, S.; Pehkonen, P.; Lakso, M.; Nass, R.; Wong, G. *Neurobiol. Dis.* **2006**, *22*, 477–86.
(222) Kuwahara, T.; Koyama, A.; Koyama, S.; Yoshina, S.; Ren, C. H.; Kato, T.; Mitani, S.; Iwatsubo, T. *Hum. Mol. Genet.* **2008**, *17*, 2997–3009.
(223) Locke, C. J.; Fox, S. A.; Caldwell, G. A.; Caldwell, K. A. *Neurosci. Lett.* **2008**, *439*, 129–33.
(224) Hamamichi, S.; Rivas, R. N.; Knight, A. L.; Cao, S.; Caldwell, K. A.; Caldwell, G. A. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 728–33.
(225) Culetto, E.; Sattelle, D. B. *Hum. Mol. Genet.* **2000**, *9*, 869–77.
(226) Baumeister, R.; Ge, L. *Trends Biotechnol.* **2002**, *20*, 147–8.
(227) Link, C. D. *Mech. Ageing Dev.* **2001**, *122*, 1639–49.
(228) Leung, M. C.; Williams, P. L.; Benedetto, A.; Au, C.; Helmcke, K. J.; Aschner, M.; Meyer, J. N. *Toxicol. Sci.* **2008**, *106*, 5–28.
(229) Shimura, H.; Hattori, N.; Kubo, S.; Mizuno, Y.; Asakawa, S.; Minoshima, S.; Shimizu, N.; Iwai, K.; Chiba, T.; Tanaka, K.; Suzuki, T. *Nat. Genet.* **2000**, *25*, 302–5.
(230) Yang, Y.; Gehrke, S.; Imai, Y.; Huang, Z.; Ouyang, Y.; Wang, J. W.; Yang, L.; Beal, M. F.; Vogel, H.; Lu, B. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 10793–8.
(231) Petrucelli, L.; O'Farrell, C.; Lockhart, P. J.; Baptista, M.; Kehoe, K.; Vink, L.; Choi, P.; Wolozin, B.; Farrer, M.; Hardy, J.; Cookson, M. R. *Neuron* **2002**, *36*, 1007–19.
(232) Yang, Y.; Nishimura, I.; Imai, Y.; Takahashi, R.; Lu, B. *Neuron* **2003**, *37*, 911–24.
(233) Zhang, Y.; Gao, J.; Chung, K. K.; Huang, H.; Dawson, V. L.; Dawson, T. M. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 13354–9.
(234) Haywood, A. F.; Staveley, B. E. *BMC Neurosci.* **2004**, *5*, 14.
(235) Yang, Y.; Gehrke, S.; Haque, M. E.; Imai, Y.; Kosek, J.; Yang, L.; Beal, M. F.; Nishimura, I.; Wakamatsu, K.; Ito, S.; Takahashi, R.; Lu, B. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 13670–5.
(236) Pesah, Y.; Pham, T.; Burgess, H.; Middlebrooks, B.; Verstreken, P.; Zhou, Y.; Harding, M.; Bellen, H.; Mardon, G. *Development* **2004**, *131*, 2183–94.
(237) Sang, T. K.; Chang, H. Y.; Lawless, G. M.; Ratnaparkhi, A.; Mee, L.; Ackerson, L. C.; Maidment, N. T.; Krantz, D. E.; Jackson, G. R. *J. Neurosci.* **2007**, *27*, 981–92.
(238) Cha, G. H.; Kim, S.; Park, J.; Lee, E.; Kim, M.; Lee, S. B.; Kim, J. M.; Chung, J.; Cho, K. S. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 10345–50.
(239) Greene, J. C.; Whitworth, A. J.; Andrews, L. A.; Parker, T. J.; Pallanck, L. J. *Hum. Mol. Genet.* **2005**, *14*, 799–811.
(240) Baptista, M. J.; Cookson, M. R.; Miller, D. W. *Neuroscientist* **2004**, *10*, 63–72.
(241) Um, J. W.; Stichel-Gunkel, C.; Lubbert, H.; Lee, G.; Chung, K. C. Mol. Cell. Neurosci., in press.
(242) Springer, W.; Hoppe, T.; Schmidt, E.; Baumeister, R. *Hum. Mol. Genet.* **2005**, *14*, 3407–23.
(243) Wilkinson, K. D. *Semin. Cell Dev. Biol.* **2000**, *11*, 141–8.
(244) Meray, R. K.; Lansbury, P. T., Jr. *J. Biol. Chem.* **2007**, *282*, 10567–75.
(245) Liu, Y.; Fallon, L.; Lashuel, H. A.; Liu, Z.; Lansbury, P. T., Jr. *Cell* **2002**, *111*, 209–18.
(246) Miyoshi, Y.; Nakayama, S.; Torikoshi, Y.; Tanaka, S.; Ishihara, H.; Taguchi, T.; Tamaki, Y.; Noguchi, S. *Cancer Sci.* **2006**, *97*, 523–9.
(247) Liu, J.; Lei, D.; Waalkes, M. P.; Beliles, R. P.; Morgan, D. L. *Toxicol. Sci.* **2003**, *74*, 174–81.
(248) Kwon, J.; Mochida, K.; Wang, Y. L.; Sekiguchi, S.; Sankai, T.; Aoki, S.; Ogura, A.; Yoshikawa, Y.; Wada, K. *Biol. Reprod.* **2005**, *73*, 29–35.
(249) Wang, Y. L.; Liu, W.; Sun, Y. J.; Kwon, J.; Setsuie, R.; Osaka, H.; Noda, M.; Aoki, S.; Yoshikawa, Y.; Wada, K. *Mol. Reprod. Dev.* **2006**, *73*, 40–9.
(250) Gong, B.; Cao, Z.; Zheng, P.; Vitolo, O. V.; Liu, S.; Staniszewski, A.; Moolman, D.; Zhang, H.; Shelanski, M.; Arancio, O. *Cell* **2006**, *126*, 775–88.
(251) Lansbury, P. T., Jr. *Cell* **2006**, *126*, 655–7.
(252) Maraganore, D. M.; Farrer, M. J.; Hardy, J. A.; Lincoln, S. J.; McDonnell, S. K.; Rocca, W. A. *Neurology* **1999**, *53*, 1858–60.
(253) Momose, Y.; Murata, M.; Kobayashi, K.; Tachikawa, M.; Nakabayashi, Y.; Kanazawa, I.; Toda, T. *Ann. Neurol.* **2002**, *51*, 133–6.
(254) Wang, J.; Zhao, C. Y.; Si, Y. M.; Liu, Z. L.; Chen, B.; Yu, L. *Mov. Disord.* **2002**, *17*, 767–71.
(255) Elbaz, A.; Levecque, C.; Clavel, J.; Vidal, J. S.; Richard, F.; Correze, J. R.; Delemotte, B.; Amouyel, P.; Alperovitch, A.; Chartier-Harlin, M. C.; Tzourio, C. *Mov. Disord.* **2003**, *18*, 130–7.
(256) Xue, S.; Jia, J. *Brain Res.* **2006**, *1087*, 28–32.
(257) Carmine Belin, A.; Westerlund, M.; Bergman, O.; Nissbrandt, H.; Lind, C.; Sydow, O.; Galter, D. Parkinsonism Relat. Disord., in press.
(258) Lincoln, S.; Vaughan, J.; Wood, N.; Baker, M.; Adamson, J.; Gwinn-Hardy, K.; Lynch, T.; Hardy, J.; Farrer, M. *Neuroreport* **1999**, *10*, 427–9.
(259) Harhangi, B. S.; Farrer, M. J.; Lincoln, S.; Bonifati, V.; Meco, G.; De Michele, G.; Brice, A.; Durr, A.; Martinez, M.; Gasser, T.; Bereznai, B.; Vaughan, J. R.; Wood, N. W.; Hardy, J.; Oostra, B. A.; Breteler, M. M. *Neurosci. Lett.* **1999**, *270*, 1–4.
(260) Mizuno, Y.; Hattori, N.; Yoshino, H.; Hatano, Y.; Satoh, K.; Tomiyama, H.; Li, Y. *J. Neural Transm.* **2006**, 191–204.
(261) Mellick, G. D.; Silburn, P. A. *Neurosci. Lett.* **2000**, *293*, 127–30.
(262) Levecque, C.; Destee, A.; Mouroux, V.; Becquet, E.; Defebvre, L.; Amouyel, P.; Chartier-Harlin, M. C. *J. Neural Transm.* **2001**, *108*, 979–84.
(263) Healy, D. G.; Abou-Sleiman, P. M.; Wood, N. W. *Cell Tissue Res.* **2004**, *318*, 189–94.
(264) Healy, D. G.; Abou-Sleiman, P. M.; Quinn, N.; Ahmadi, K. R.; Ozawa, T.; Kamm, C.; Wullner, U.; Oertel, W. H.; Burk, K.; Dupont, E.; Pellecchia, M. T.; Tolosa, E.; Gasser, T.; Holton, J. L.; Revesz, T.; Goldstein, D. B.; Lees, A. J.; Wood, N. W. *Mov. Disord.* **2005**, *20*, 1338–43.
(265) Healy, D. G.; Abou-Sleiman, P. M.; Casas, J. P.; Ahmadi, K. R.; Lynch, T.; Gandhi, S.; Muqit, M. M.; Foltynie, T.; Barker, R.; Bhatia, K. P.; Quinn, N. P.; Lees, A. J.; Gibson, J. M.; Holton, J. L.; Revesz, T.; Goldstein, D. B.; Wood, N. W. *Ann. Neurol.* **2006**, *59*, 627–33.

(266) Naze, P.; Vuillaume, I.; Destee, A.; Pasquier, F.; Sablonniere, B. *Neurosci. Lett.* **2002**, *328*, 1–4.
(267) Barrachina, M.; Castano, E.; Dalfo, E.; Maes, T.; Buesa, C.; Ferrer, I. *Neurobiol. Dis.* **2006**, *22*, 265–73.
(268) Saigoh, K.; Wang, Y. L.; Suh, J. G.; Yamanishi, T.; Sakai, Y.; Kiyosawa, H.; Harada, T.; Ichihara, N.; Wakana, S.; Kikuchi, T.; Wada, K. *Nat. Genet.* **1999**, *23*, 47–51.
(269) Setsuie, R.; Wang, Y. L.; Mochizuki, H.; Osaka, H.; Hayakawa, H.; Ichihara, N.; Li, H.; Furuta, A.; Sano, Y.; Sun, Y. J.; Kwon, J.; Kabuta, T.; Yoshimi, K.; Aoki, S.; Mizuno, Y.; Noda, M.; Wada, K. *Neurochem. Int.* **2007**, *50*, 119–29.
(270) Ardley, H. C.; Scott, G. B.; Rose, S. A.; Tan, N. G.; Robinson, P. A. *J. Neurochem.* **2004**, *90*, 379–91.
(271) Wang, Y. L.; Takeda, A.; Osaka, H.; Hara, Y.; Furuta, A.; Setsuie, R.; Sun, Y. J.; Kwon, J.; Sato, Y.; Sakurai, M.; Noda, M.; Yoshikawa, Y.; Wada, K. *Brain Res.* **2004**, *1019*, 1–9.
(272) Sakurai, M.; Ayukawa, K.; Setsuie, R.; Nishikawa, K.; Hara, Y.; Ohashi, H.; Nishimoto, M.; Abe, T.; Kudo, Y.; Sekiguchi, M.; Sato, Y.; Aoki, S.; Noda, M.; Wada, K. *J. Cell Sci.* **2006**, *119*, 162–71.
(273) Doss-Pepe, E. W.; Chen, L.; Madura, K. *J. Biol. Chem.* **2005**, *280*, 16619–24.
(274) Bifsha, P.; Landry, K.; Ashmarina, L.; Durand, S.; Seyrantepe, V.; Trudel, S.; Quiniou, C.; Chemtob, S.; Xu, Y.; Gravel, R. A.; Sladek, R.; Pshezhetsky, A. V. *Cell Death Differ.* **2007**, *14*, 511–23.
(275) Kabuta, T.; Wada, K. *Autophagy* **2008**, *4*, 827–9.
(276) Liu, Z.; Meray, R. K.; Grammatopoulos, T. N.; Fredenburg, R. A.; Cookson, M. R.; Liu, Y.; Logan, T.; Lansbury, P. T., Jr. Proc. Natl. Acad. Sci. U. S. A., in press.
(277) Manago, Y.; Kanahori, Y.; Shimada, A.; Sato, A.; Amano, T.; Sato-Sano, Y.; Setsuie, R.; Sakurai, M.; Aoki, S.; Wang, Y. L.; Osaka, H.; Wada, K.; Noda, M. *J. Neurochem.* **2005**, *92*, 1061–72.
(278) Kurihara, L. J.; Kikuchi, T.; Wada, K.; Tilghman, S. M. *Hum. Mol. Genet.* **2001**, *10*, 1963–70.
(279) Kurihara, L. J.; Semenova, E.; Levorse, J. M.; Tilghman, S. M. *Mol. Cell. Biol.* **2000**, *20*, 2498–504.
(280) Larsen, C. N.; Price, J. S.; Wilkinson, K. D. *Biochemistry* **1996**, *35*, 6735–44.
(281) Li, Z.; Melandri, F.; Berdo, I.; Jansen, M.; Hunter, L.; Wright, S.; Valbrun, D.; Figueiredo-Pereira, M. E. *Biochem. Biophys. Res. Commun.* **2004**, *319*, 1171–80.
(282) Kwon, J.; Sekiguchi, S.; Wang, Y. L.; Setsuie, R.; Yoshikawa, Y.; Wada, K. *Exp. Anim.* **2006**, *55*, 35–43.
(283) Kwon, J.; Wang, Y. L.; Setsuie, R.; Sekiguchi, S.; Sato, Y.; Sakurai, M.; Noda, M.; Aoki, S.; Yoshikawa, Y.; Wada, K. *Am. J. Pathol.* **2004**, *165*, 1367–74.
(284) Chiaki Fujitake, M. T.; Inoue, H.; Takahashi, K. East Asia Worm Meeting 111, 2004.
(285) Beilina, A.; Van Der Brug, M.; Ahmad, R.; Kesavapany, S.; Miller, D. W.; Petsko, G. A.; Cookson, M. R. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 5703–8.
(286) Zhou, C.; Huang, Y.; Shao, Y.; May, J.; Prou, D.; Perier, C.; Dauer, W.; Schon, E. A.; Przedborski, S. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 12022–7.
(287) Weihofen, A.; Ostaszewski, B.; Minami, Y.; Selkoe, D. J. *Hum. Mol. Genet.* **2008**, *17*, 602–16.
(288) Moriwaki, Y.; Kim, Y. J.; Ido, Y.; Misawa, H.; Kawashima, K.; Endo, S.; Takahashi, R. *Neurosci. Res.* **2008**, *61*, 43–8.
(289) Kim, Y.; Park, J.; Kim, S.; Song, S.; Kwon, S. K.; Lee, S. H.; Kitada, T.; Kim, J. M.; Chung, J. *Biochem. Biophys. Res. Commun.* **2008**, *377*, 975–80.
(290) Petit, A.; Kawarai, T.; Paitel, E.; Sanjo, N.; Maj, M.; Scheid, M.; Chen, F.; Gu, Y.; Hasegawa, H.; Salehi-Rad, S.; Wang, L.; Rogaeva, E.; Fraser, P.; Robinson, B.; St George-Hyslop, P.; Tandon, A. *J. Biol. Chem.* **2005**, *280*, 34025–32.
(291) Wood-Kaczmar, A.; Gandhi, S.; Yao, Z.; Abramov, A. S.; Miljan, E. A.; Keen, G.; Stanyer, L.; Hargreaves, I.; Klupsch, K.; Deas, E.; Downward, J.; Mansfield, L.; Jat, P.; Taylor, J.; Heales, S.; Duchen, M. R.; Latchman, D.; Tabrizi, S. J.; Wood, N. W. *PLoS One* **2008**, *3*, e2455.
(292) Todd, A. M.; Staveley, B. E. *Genome* **2008**, *51*, 1040–6.
(293) Haque, M. E.; Thomas, K. J.; D'Souza, C.; Callaghan, S.; Kitada, T.; Slack, R. S.; Fraser, P.; Cookson, M. R.; Tandon, A.; Park, D. S. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 1716–21.
(294) Marongiu, R.; Spencer, B.; Crews, L.; Adame, A.; Patrick, C.; Trejo, M.; Dallapiccola, B.; Valente, E. M.; Masliah, E. *J. Neurochem.* **2009**, *108*, 1561–74.
(295) Gautier, C. A.; Kitada, T.; Shen, J. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 11364–9.
(296) Liu, W.; Vives-Bauza, C.; Acin-Perez, R.; Yamamoto, A.; Tan, Y.; Li, Y.; Magrane, J.; Stavarache, M. A.; Shaffer, S.; Chang, S.; Kaplitt, M. G.; Huang, X. Y.; Beal, M. F.; Manfredi, G.; Li, C. *PLoS One* **2009**, *4*, e4597.
(297) Anichtchik, O.; Diekmann, H.; Fleming, A.; Roach, A.; Goldsmith, P.; Rubinsztein, D. C. *J. Neurosci.* **2008**, *28*, 8199–207.
(298) Wang, H. L.; Chou, A. H.; Yeh, T. H.; Li, A. H.; Chen, Y. L.; Kuo, Y. L.; Tsai, S. R.; Yu, S. T. *Neurobiol. Dis.* **2007**, *28*, 216–26.
(299) Yang, Y.; Ouyang, Y.; Yang, L.; Beal, M. F.; McQuibban, A.; Vogel, H.; Lu, B. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 7070–5.
(300) Park, J.; Lee, G.; Chung, J. *Biochem. Biophys. Res. Commun.* **2009**, *378*, 518–23.
(301) Samann, J.; Hegermann, J.; Gromoff, E. V.; Eimer, S.; Baumeister, R.; Schmidt, E. J. Biol. Chem., in press.
(302) Nagakubo, D.; Taira, T.; Kitaura, H.; Ikeda, M.; Tamai, K.; Iguchi-Ariga, S. M.; Ariga, H. *Biochem. Biophys. Res. Commun.* **1997**, *231*, 509–13.
(303) Bandyopadhyay, S.; Cookson, M. R. *BMC Evol. Biol.* **2004**, *4*, 6.
(304) Hague, S.; Rogaeva, E.; Hernandez, D.; Gulick, C.; Singleton, A.; Hanson, M.; Johnson, J.; Weiser, R.; Gallardo, M.; Ravina, B.; Gwinn-Hardy, K.; Crawley, A.; St George-Hyslop, P. H.; Lang, A. E.; Heutink, P.; Bonifati, V.; Hardy, J.; Singleton, A. *Ann. Neurol.* **2003**, *54*, 271–4.
(305) Abou-Sleiman, P. M.; Healy, D. G.; Quinn, N.; Lees, A. J.; Wood, N. W. *Ann. Neurol.* **2003**, *54*, 283–6.
(306) Bonifati, V.; Rizzu, P.; van Baren, M. J.; Schaap, O.; Breedveld, G. J.; Krieger, E.; Dekker, M. C.; Squitieri, F.; Ibanez, P.; Joosse, M.; van Dongen, J. W.; Vanacore, N.; van Swieten, J. C.; Brice, A.; Meco, G.; van Duijn, C. M.; Oostra, B. A.; Heutink, P. *Science* **2003**, *299*, 256–9.
(307) Clark, L. N.; Afridi, S.; Mejia-Santana, H.; Harris, J.; Louis, E. D.; Cote, L. J.; Andrews, H.; Singleton, A.; Wavrant De-Vrieze, F.; Hardy, J.; Mayeux, R.; Fahn, S.; Waters, C.; Ford, B.; Frucht, S.; Ottman, R.; Marder, K. *Mov. Disord.* **2004**, *19*, 796–800.
(308) Bonifati, V.; Oostra, B. A.; Heutink, P. *J. Mol. Med. (Berlin, Germany)* **2004**, *82*, 163–74.
(309) Hedrich, K.; Schafer, N.; Hering, R.; Hagenah, J.; Lanthaler, A. J.; Schwinger, E.; Kramer, P. L.; Ozelius, L. J.; Bressman, S. B.; Abbruzzese, G.; Martinelli, P.; Kostic, V.; Pramstaller, P. P.; Vieregge, P.; Riess, O.; Klein, C. *Ann. Neurol.* **2004**, *55*, 145. Author reply: 145−6.
(310) Annesi, G.; Savettieri, G.; Pugliese, P.; D'Amelio, M.; Tarantino, P.; Ragonese, P.; La Bella, V.; Piccoli, T.; Civitelli, D.; Annesi, F.; Fierro, B.; Piccoli, F.; Arabia, G.; Caracciolo, M.; Ciro Candiano, I. C.; Quattrone, A. *Ann. Neurol.* **2005**, *58*, 803–7.
(311) Hod, Y.; Pentyala, S. N.; Whyard, T. C.; El-Maghrabi, M. R. *J. Cell Biochem.* **1999**, *72*, 435–44.
(312) Mitsumoto, A.; Nakagawa, Y. *Free Radical Res.* **2001**, *35*, 885–93.
(313) Mitsumoto, A.; Nakagawa, Y.; Takeuchi, A.; Okawa, K.; Iwamatsu, A.; Takanezawa, Y. *Free Radical Res.* **2001**, *35*, 301–10.
(314) Lev, N.; Ickowicz, D.; Barhum, Y.; Lev, S.; Melamed, E.; Offen, D. *J. Neural Transm.* **2009**, *116*, 151–60.
(315) Andres-Mateos, E.; Perier, C.; Zhang, L.; Blanchard-Fillion, B.; Greco, T. M.; Thomas, B.; Ko, H. S.; Sasaki, M.; Ischiropoulos, H.; Przedborski, S.; Dawson, T. M.; Dawson, V. L. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 14807–12.
(316) Ooe, H.; Iguchi-Ariga, S. M.; Ariga, H. *Neurosci. Lett.* **2006**, *404*, 166–9.
(317) Canet-Aviles, R. M.; Wilson, M. A.; Miller, D. W.; Ahmad, R.; McLendon, C.; Bandyopadhyay, S.; Baptista, M. J.; Ringe, D.; Petsko, G. A.; Cookson, M. R. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 9103–8.
(318) Ooe, H.; Taira, T.; Iguchi-Ariga, S. M.; Ariga, H. *Toxicol. Sci.* **2005**, *88*, 114–26.
(319) Kim, R. H.; Smith, P. D.; Aleyasin, H.; Hayley, S.; Mount, M. P.; Pownall, S.; Wakeham, A.; You-Ten, A. J.; Kalia, S. K.; Horne, P.; Westaway, D.; Lozano, A. M.; Anisman, H.; Park, D. S.; Mak, T. W. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 5215–20.
(320) Mullett, S. J.; Hinkle, D. A. *Neurobiol. Dis.* **2009**, *33*, 28–36.
(321) Zhou, W.; Freed, C. R. *J. Biol. Chem.* **2005**, *280*, 43150–8.
(322) Li, H. M.; Niki, T.; Taira, T.; Iguchi-Ariga, S. M.; Ariga, H. *Free Radical Res.* **2005**, *39*, 1091–9.
(323) Cookson, M. R. *Annu. Rev. Biochem.* **2005**, *74*, 29–52.
(324) Xu, J.; Zhong, N.; Wang, H.; Elias, J. E.; Kim, C. Y.; Woldman, I.; Pifl, C.; Gygi, S. P.; Geula, C.; Yankner, B. A. *Hum. Mol. Genet.* **2005**, *14*, 1231–41.
(325) Blackinton, J.; Kumaran, R.; van der Brug, M. P.; Ahmad, R.; Olson, L.; Galter, D.; Lees, A.; Bandopadhyay, R.; Cookson, M. R. *Neurosci. Lett.* **2009**, *452*, 8–11.
(326) Shendelman, S.; Jonason, A.; Martinat, C.; Leete, T.; Abeliovich, A. *PLoS Biol.* **2004**, *2*, e362.
(327) Choi, J.; Sullards, M. C.; Olzmann, J. A.; Rees, H. D.; Weintraub, S. T.; Bostwick, D. E.; Gearing, M.; Levey, A. I.; Chin, L. S.; Li, L. *J. Biol. Chem.* **2006**, *281*, 10816–24.
(328) Shinbo, Y.; Niki, T.; Taira, T.; Ooe, H.; Takahashi-Niki, K.; Maita, C.; Seino, C.; Iguchi-Ariga, S. M.; Ariga, H. *Cell Death Differ.* **2006**, *13*, 96–108.

(329) Zhou, Z. D.; Kerk, S. Y.; Xiong, G. G.; Lim, T. M. *J. Neurochem.* **2009**, *108*, 601–10.
(330) Zimprich, A.; Biskup, S.; Leitner, P.; Lichtner, P.; Farrer, M.; Lincoln, S.; Kachergus, J.; Hulihan, M.; Uitti, R. J.; Calne, D. B.; Stoessl, A. J.; Pfeiffer, R. F.; Patenge, N.; Carbajal, I. C.; Vieregge, P.; Asmus, F.; Muller-Myhsok, B.; Dickson, D. W.; Meitinger, T.; Strom, T. M.; Wszolek, Z. K.; Gasser, T. *Neuron* **2004**, *44*, 601–7.
(331) Xiromerisiou, G.; Hadjigeorgiou, G. M.; Gourbali, V.; Johnson, J.; Papakonstantinou, I.; Papadimitriou, A.; Singleton, A. B. *Eur. J. Neurol.* **2007**, *14*, 7–11.
(332) Wu, T.; Zeng, Y.; Ding, X.; Li, X.; Li, W.; Dong, H.; Chen, S.; Zhang, X.; Ma, G.; Yao, J.; Deng, X. *Neuroreport* **2006**, *17*, 1859–62.
(333) Tan, E. K.; Lim, H. Q.; Yuen, Y.; Zhao, Y. *Mov. Disord.* **2008**, *23*, 734–6.
(334) Covy, J. P.; Yuan, W.; Waxman, E. A.; Hurtig, H. I.; Van Deerlin, V. M.; Giasson, B. I. *Mov. Disord.* **2009**, *24*, 32–9.
(335) Berg, D.; Schweitzer, K.; Leitner, P.; Zimprich, A.; Lichtner, P.; Belcredi, P.; Brussel, T.; Schulte, C.; Maass, S.; Nagele, T. *Brain* **2005**, *128*, 3000–11.
(336) Skipper, L.; Shen, H.; Chua, E.; Bonnard, C.; Kolatkar, P.; Tan, L. C.; Jamora, R. D.; Puvan, K.; Puong, K. Y.; Zhao, Y.; Pavanni, R.; Wong, M. C.; Yuen, Y.; Farrer, M.; Liu, J. J.; Tan, E. K. *Neurology* **2005**, *65*, 1319–21.
(337) Paisan-Ruiz, C.; Lang, A. E.; Kawarai, T.; Sato, C.; Salehi-Rad, S.; Fisman, G. K.; Al-Khairallah, T.; St George-Hyslop, P.; Singleton, A.; Rogaeva, E. Neurology, in press.
(338) Nuytemans, K.; Rademakers, R.; Theuns, J.; Pals, P.; Engelborghs, S.; Pickut, B.; de Pooter, T.; Peeters, K.; Mattheijssens, M.; Van den Broeck, M.; Cras, P.; De Deyn, P. P.; van Broeckhoven, C. *Eur. J. Hum. Genet.* **2008**, *16*, 471–9.
(339) Mata, I. F.; Taylor, J. P.; Kachergus, J.; Hulihan, M.; Huerta, C.; Lahoz, C.; Blazquez, M.; Guisasola, L. M.; Salvador, C.; Ribacoba, R.; Martinez, C.; Farrer, M.; Alvarez, V. *Neurosci. Lett.* **2005**, *382*, 309–11.
(340) Nichols, W. C.; Marek, D. K.; Pauciulo, M. W.; Pankratz, N.; Halter, C. A.; Rudolph, A.; Shults, C. W.; Wojcieszek, J.; Foroud, T. *Mov. Disord.* **2007**, *22*, 254–7.
(341) Tan, E. K.; Tan, L. C.; Lim, H. Q.; Li, R.; Tang, M.; Yih, Y.; Pavanni, R.; Prakash, K. M.; Fook-Chong, S.; Zhao, Y. *Hum. Genet.* **2008**, *124*, 287–8.
(342) Mata, I. F.; Kachergus, J. M.; Taylor, J. P.; Lincoln, S.; Aasly, J.; Lynch, T.; Hulihan, M. M.; Cobb, S. A.; Wu, R. M.; Lu, C. S.; Lahoz, C.; Wszolek, Z. K.; Farrer, M. J. *Neurogenetics* **2005**, *6*, 171–7.
(343) Khan, N. L.; Jain, S.; Lynch, J. M.; Pavese, N.; Abou-Sleiman, P.; Holton, J. L.; Healy, D. G.; Gilks, W. P.; Sweeney, M. G.; Ganguly, M.; Gibbons, V.; Gandhi, S.; Vaughan, J.; Eunson, L. H.; Katzenschlager, R.; Gayton, J.; Lennox, G.; Revesz, T.; Nicholl, D.; Bhatia, K. P.; Quinn, N.; Brooks, D.; Lees, A. J.; Davis, M. B.; Piccini, P.; Singleton, A. B.; Wood, N. W. *Brain* **2005**, *128*, 2786–96.
(344) Lu, C. S.; Simons, E. J.; Wu-Chou, Y. H.; Fonzo, A. D.; Chang, H. C.; Chen, R. S.; Weng, Y. H.; Rohe, C. F.; Breedveld, G. J.; Hattori, N.; Gasser, T.; Oostra, B. A.; Bonifati, V. *Parkinsonism Relat. Disord.* **2005**, *11*, 521–2.
(345) Kachergus, J.; Mata, I. F.; Hulihan, M.; Taylor, J. P.; Lincoln, S.; Aasly, J.; Gibson, J. M.; Ross, O. A.; Lynch, T.; Wiley, J.; Payami, H.; Nutt, J.; Maraganore, D. M.; Czyzewski, K.; Styczynska, M.; Wszolek, Z. K.; Farrer, M. J.; Toft, M. *Am. J. Hum. Genet.* **2005**, *76*, 672–80.
(346) Patra, B.; Parsian, A. J.; Racette, B. A.; Zhao, J. H.; Perlmutter, J. S.; Parsian, A. *Parkinsonism Relat. Disord.* **2009**, *15*, 175–80.
(347) Pirkevi, C.; Lesage, S.; Condroyer, C.; Tomiyama, H.; Hattori, N.; Ertan, S.; Brice, A.; Basak, A. N. Neurogenetics, in press.
(348) Tan, E. K.; Yew, K.; Chua, E.; Puvan, K.; Shen, H.; Lee, E.; Puong, K. Y.; Zhao, Y.; Pavanni, R.; Wong, M. C.; Jamora, D.; de Silva, D.; Moe, K. T.; Woon, F. P.; Yuen, Y.; Tan, L. *Mov. Disord.* **2006**, *21*, 789–93.
(349) An, X. K.; Peng, R.; Li, T.; Burgunder, J. M.; Wu, Y.; Chen, W. J.; Zhang, J. H.; Wang, Y. C.; Xu, Y. M.; Gou, Y. R.; Yuan, G. G.; Zhang, Z. J. *Eur. J. Neurol.* **2008**, *15*, 301–5.
(350) Taylor, J. P.; Hulihan, M. M.; Kachergus, J. M.; Melrose, H. L.; Lincoln, S. J.; Hinkle, K. M.; Stone, J. T.; Ross, O. A.; Hauser, R.; Aasly, J.; Gasser, T.; Payami, H.; Wszolek, Z. K.; Farrer, M. J. *Neurogenetics* **2007**, *8*, 95–102.
(351) Skipper, L.; Li, Y.; Bonnard, C.; Pavanni, R.; Yih, Y.; Chua, E.; Sung, W. K.; Tan, L.; Wong, M. C.; Tan, E. K.; Liu, J. *Hum. Mol. Genet.* **2005**, *14*, 3549–56.
(352) Ozelius, L. J.; Senthil, G.; Saunders-Pullman, R.; Ohmann, E.; Deligtisch, A.; Tagliati, M.; Hunt, A. L.; Klein, C.; Henick, B.; Hailpern, S. M.; Lipton, R. B.; Soto-Valencia, J.; Risch, N.; Bressman, S. B. *N. Engl. J. Med.* **2006**, *354*, 424–5.
(353) Gilks, W. P.; Abou-Sleiman, P. M.; Gandhi, S.; Jain, S.; Singleton, A.; Lees, A. J.; Shaw, K.; Bhatia, K. P.; Bonifati, V.; Quinn, N. P.; Lynch, J.; Healy, D. G.; Holton, J. L.; Revesz, T.; Wood, N. W. *Lancet* **2005**, *365*, 415–6.
(354) Di Fonzo, A.; Rohe, C. F.; Ferreira, J.; Chien, H. F.; Vacca, L.; Stocchi, F.; Guedes, L.; Fabrizio, E.; Manfredi, M.; Vanacore, N.; Goldwurm, S.; Breedveld, G.; Sampaio, C.; Meco, G.; Barbosa, E.; Oostra, B. A.; Bonifati, V. *Lancet* **2005**, *365*, 412–5.
(355) Nichols, W. C.; Pankratz, N.; Hernandez, D.; Paisan-Ruiz, C.; Jain, S.; Halter, C. A.; Michaels, V. E.; Reed, T.; Rudolph, A.; Shults, C. W.; Singleton, A.; Foroud, T. *Lancet* **2005**, *365*, 410–2.
(356) Spanaki, C.; Latsoudis, H.; Plaitakis, A. *Neurology* **2006**, *67*, 1518–9.
(357) Lesage, S.; Janin, S.; Lohmann, E.; Leutenegger, A. L.; Leclere, L.; Viallet, F.; Pollak, P.; Durif, F.; Thobois, S.; Layet, V.; Vidailhet, M.; Agid, Y.; Durr, A.; Brice, A.; Bonnet, A. M.; Borg, M.; Broussolle, E.; Damier, P.; Destee, A.; Martinez, M.; Penet, C.; Rasco, O.; Tison, F.; Tranchan, C.; Verin, M. *Arch. Neurol.* **2007**, *64*, 425–30.
(358) Ishihara, L.; Gibson, R. A.; Warren, L.; Amouri, R.; Lyons, K.; Wielinski, C.; Hunter, C.; Swartz, J. E.; Elango, R.; Akkari, P. A.; Leppert, D.; Surh, L.; Reeves, K. H.; Thomas, S.; Ragone, L.; Hattori, N.; Pahwa, R.; Jankovic, J.; Nance, M.; Freeman, A.; Gouider-Khouja, N.; Kefi, M.; Zouari, M.; Ben Sassi, S.; Ben Yahmed, S.; El Euch-Fayeche, G.; Middleton, L.; Burn, D. J.; Watts, R. L.; Hentati, F. *Mov. Disord.* **2007**, *22*, 55–61.
(359) Goldwurm, S.; Zini, M.; Mariani, L.; Tesei, S.; Miceli, R.; Sironi, F.; Clementi, M.; Bonifati, V.; Pezzoli, G. *Neurology* **2007**, *68*, 1141–3.
(360) Floris, G.; Cannas, A.; Solla, P.; Murru, M. R.; Tranquilli, S.; Corongiu, D.; Rolesu, M.; Cuccu, S.; Sardu, C.; Marrosu, F.; Marrosu, M. G. Parkinsonism Relat. Disord., in press.
(361) Gasser, T. *Curr. Opin. Neurol.* **2005**, *18*, 363–9.
(362) Goldwurm, S.; Di Fonzo, A.; Simons, E. J.; Rohe, C. F.; Zini, M.; Canesi, M.; Tesei, S.; Zecchinelli, A.; Antonini, A.; Mariani, C.; Meucci, N.; Sacilotto, G.; Sironi, F.; Salani, G.; Ferreira, J.; Chien, H. F.; Fabrizio, E.; Vanacore, N.; Dalla Libera, A.; Stocchi, F.; Diroma, C.; Lamberti, P.; Sampaio, C.; Meco, G.; Barbosa, E.; Bertoli-Avella, A. M.; Breedveld, G. J.; Oostra, B. A.; Pezzoli, G.; Bonifati, V. *J. Med. Genet.* **2005**, *42*, e65.
(363) Gosal, D.; Ross, O. A.; Wiley, J.; Irvine, G. B.; Johnston, J. A.; Toft, M.; Mata, I. F.; Kachergus, J.; Hulihan, M.; Taylor, J. P.; Lincoln, S. J.; Farrer, M. J.; Lynch, T.; Mark Gibson, J. *Parkinsonism Relat. Disord.* **2005**, *11*, 349–52.
(364) Haugarvoll, K.; Rademakers, R.; Kachergus, J. M.; Nuytemans, K.; Ross, O. A.; Gibson, J. M.; Tan, E. K.; Gaig, C.; Tolosa, E.; Goldwurm, S.; Guidi, M.; Riboldazzi, G.; Brown, L.; Walter, U.; Benecke, R.; Berg, D.; Gasser, T.; Theuns, J.; Pals, P.; Cras, P.; De Deyn, P. P.; Engelborghs, S.; Pickut, B.; Uitti, R. J.; Foroud, T.; Nichols, W. C.; Hagenah, J.; Klein, C.; Samii, A.; Zabetian, C. P.; Bonifati, V.; Van Broeckhoven, C.; Farrer, M. J.; Wszolek, Z. K. *Neurology* **2008**, *70*, 1456–60.
(365) Gandhi, P. N.; Chen, S. G.; Wilson-Delfosse, A. L. J. Neurosci. Res., in press.
(366) Tan, E. K.; Skipper, L.; Chua, E.; Wong, M. C.; Pavanni, R.; Bonnard, C.; Kolatkar, P.; Liu, J. J. *Mov. Disord.* **2006**, *21*, 997–1001.
(367) Chen-Plotkin, A. S.; Yuan, W.; Anderson, C.; McCarty Wood, E.; Hurtig, H. I.; Clark, C. M.; Miller, B. L.; Lee, V. M.; Trojanowski, J. Q.; Grossman, M.; Van Deerlin, V. M. *Neurology* **2008**, *70*, 521–7.
(368) Nandhagopal, R.; Mak, E.; Schulzer, M.; McKenzie, J.; McCormick, S.; Sossi, V.; Ruth, T. J.; Strongosky, A.; Farrer, M. J.; Wszolek, Z. K.; Stoessl, A. J. *Neurology* **2008**, *71*, 1790–5.
(369) Ito, G.; Okai, T.; Fujino, G.; Takeda, K.; Ichijo, H.; Katada, T.; Iwatsubo, T. *Biochemistry* **2007**, *46*, 1380–8.
(370) Lewis, P. A. *Biol. Cell* **2009**, *101*, 183–91.
(371) Westerlund, M.; Belin, A. C.; Anvret, A.; Bickford, P.; Olson, L.; Galter, D. *Neuroscience* **2008**, *152*, 429–36.
(372) Higashi, S.; Moore, D. J.; Colebrooke, R. E.; Biskup, S.; Dawson, V. L.; Arai, H.; Dawson, T. M.; Emson, P. C. *J. Neurochem.* **2007**, *100*, 368–81.
(373) Han, B. S.; Iacovitti, L.; Katano, T.; Hattori, N.; Seol, W.; Kim, K. S. *Neurosci. Lett.* **2008**, *442*, 190–4.
(374) Smith, W. W.; Pei, Z.; Jiang, H.; Moore, D. J.; Liang, Y.; West, A. B.; Dawson, V. L.; Dawson, T. M.; Ross, C. A. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 18676–81.
(375) Hatano, T.; Kubo, S.; Imai, S.; Maeda, M.; Ishikawa, K.; Mizuno, Y.; Hattori, N. *Hum. Mol. Genet.* **2007**, *16*, 678–90.
(376) Zhu, X.; Siedlak, S. L.; Smith, M. A.; Perry, G.; Chen, S. G. *Ann. Neurol.* **2006**, *60*, 617–8. Author reply: 618−9.
(377) Alegre-Abarrategui, J.; Ansorge, O.; Esiri, M.; Wade-Martins, R. *Neuropathol. Appl. Neurobiol.* **2008**, *34*, 272–83.
(378) Mata, I. F.; Wedemeyer, W. J.; Farrer, M. J.; Taylor, J. P.; Gallo, K. A. *Trends Neurosci.* **2006**, *29*, 286–93.

(379) Gloeckner, C. J.; Kinkl, N.; Schumacher, A.; Braun, R. J.; O'Neill, E.; Meitinger, T.; Kolch, W.; Prokisch, H.; Ueffing, M. *Hum. Mol. Genet.* **2006**, *15*, 223–32.
(380) Greggio, E.; Jain, S.; Kingsbury, A.; Bandopadhyay, R.; Lewis, P.; Kaganovich, A.; van der Brug, M. P.; Beilina, A.; Blackinton, J.; Thomas, K. J.; Ahmad, R.; Miller, D. W.; Kesavapany, S.; Singleton, A.; Lees, A.; Harvey, R. J.; Harvey, K.; Cookson, M. R. *Neurobiol. Dis.* **2006**, *23*, 329–41.
(381) White, L. R.; Toft, M.; Kvam, S. N.; Farrer, M. J.; Aasly, J. O. *J. Neurosci. Res.* **2007**, *85*, 1288–1294.
(382) Plowey, E. D.; Cherra, S. J., 3rd; Liu, Y. J.; Chu, C. T. *J. Neurochem.* **2008**, *105*, 1048–56.
(383) Gandhi, P. N.; Wang, X.; Zhu, X.; Chen, S. G.; Wilson-Delfosse, A. L. *J. Neurosci. Res.* **2008**, *86*, 1711–20.
(384) Deng, J.; Lewis, P. A.; Greggio, E.; Sluch, E.; Beilina, A.; Cookson, M. R. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 1499–504.
(385) Weiss, B. *Sci. Signal* **2008**, *1*, pe27.
(386) Zabetian, C. P.; Hutter, C. M.; Yearout, D.; Lopez, A. N.; Factor, S. A.; Griffith, A.; Leis, B. C.; Bird, T. D.; Nutt, J. G.; Higgins, D. S.; Roberts, J. W.; Kay, D. M.; Edwards, K. L.; Samii, A.; Payami, H. *Am. J. Hum. Genet.* **2006**, *79*, 752–8.
(387) Ohta, E.; Hasegawa, K.; Gasser, T.; Obata, F. *Neurosci. Lett.* **2007**, *417*, 21–3.
(388) Covy, J. P.; Giasson, B. I. *Biochem. Biophys. Res. Commun.* **2009**, *378*, 473–7.
(389) Anand, V. S.; Reichling, L. J.; Lipinski, K.; Stochaj, W.; Duan, W.; Kelleher, K.; Pungaliya, P.; Brown, E. L.; Reinhart, P. H.; Somberg, R.; Hirst, W. D.; Riddle, S. M.; Steven, P. B. *FEBS J.* **2009**, *276*, 466–78.
(390) Dachsel, J. C.; Taylor, J. P.; Mok, S. S.; Ross, O. A.; Hinkle, K. M.; Bailey, R. M.; Hines, J. H.; Szutu, J.; Madden, B.; Petrucelli, L.; Farrer, M. J. Parkinsonism Relat. Disord., in press.
(391) Ho, C. C.; Rideout, H. J.; Ribe, E.; Troy, C. M.; Dauer, W. T. *J. Neurosci.* **2009**, *29*, 1011–6.
(392) Shin, N.; Jeong, H.; Kwon, J.; Heo, H. Y.; Kwon, J. J.; Yun, H. J.; Kim, C. H.; Han, B. S.; Tong, Y.; Shen, J.; Hatano, T.; Hattori, N.; Kim, K. S.; Chang, S.; Seol, W. *Exp. Cell Res.* **2008**, *314*, 2055–65.
(393) Habig, K.; Walter, M.; Poths, S.; Riess, O.; Bonin, M. *Neurogenetics* **2008**, *9*, 83–94.
(394) Wang, D.; Tang, B.; Zhao, G.; Pan, Q.; Xia, K.; Bodmer, R.; Zhang, Z. *Mol. Neurodegener.* **2008**, *3*, 3.
(395) Liu, Z.; Wang, X.; Yu, Y.; Li, X.; Wang, T.; Jiang, H.; Ren, Q.; Jiao, Y.; Sawa, A.; Moran, T.; Ross, C. A.; Montell, C.; Smith, W. W. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 2693–8.
(396) Sakaguchi-Nakashima, A.; Meir, J. Y.; Jin, Y.; Matsumoto, K.; Hisamoto, N. *Curr. Biol.* **2007**, *17*, 592–8.
(397) Williams, D. R.; Hadeed, A.; al-Din, A. S.; Wreikat, A. L.; Lees, A. J. *Mov. Disord.* **2005**, *20*, 1264–71.
(398) Schneider, S. A.; Bhatia, K. P.; Hardy, J. Mov. Disord., in press.
(399) Ning, Y. P.; Kanai, K.; Tomiyama, H.; Li, Y.; Funayama, M.; Yoshino, H.; Sato, S.; Asahina, M.; Kuwabara, S.; Takeda, A.; Hattori, T.; Mizuno, Y.; Hattori, N. *Neurology* **2008**, *70*, 1491–3.
(400) Lin, C. H.; Tan, E. K.; Chen, M. L.; Tan, L. C.; Lim, H. Q.; Chen, G. S.; Wu, R. M. *Neurology* **2008**, *71*, 1727–32.
(401) Guo, J. F.; Xiao, B.; Liao, B.; Zhang, X. W.; Nie, L. L.; Zhang, Y. H.; Shen, L.; Jiang, H.; Xia, K.; Pan, Q.; Yan, X. X.; Tang, B. S. *Mov. Disord.* **2008**, *23*, 2074–9.
(402) Lees, A. J.; Singleton, A. B. *Neurology* **2007**, *68*, 1553–4.
(403) Di Fonzo, A.; Chien, H. F.; Socal, M.; Giraudo, S.; Tassorelli, C.; Iliceto, G.; Fabbrini, G.; Marconi, R.; Fincati, E.; Abbruzzese, G.; Marini, P.; Squitieri, F.; Horstink, M. W.; Montagna, P.; Libera, A. D.; Stocchi, F.; Goldwurm, S.; Ferreira, J. J.; Meco, G.; Martignoni, E.; Lopiano, L.; Jardim, L. B.; Oostra, B. A.; Barbosa, E. R.; Bonifati, V. *Neurology* **2007**, *68*, 1557–62.
(404) Vilarino-Guell, C.; Soto, A. I.; Lincoln, S. J.; Yahmed, S. B.; Kefi, M.; Heckman, M. G.; Hulihan, M. M.; Chai, H.; Diehl, N. N.; Amouri, R.; Rajput, A.; Mash, D. C.; Dickson, D. W.; Middleton, L. T.; Gibson, R. A.; Hentati, F.; Farrer, M. J. *Hum. Mutat.* **2009**, *30*, 406–10.
(405) Tomiyama, H.; Kokubo, Y.; Sasaki, R.; Li, Y.; Imamichi, Y.; Funayama, M.; Mizuno, Y.; Hattori, N.; Kuzuhara, S. *Mov. Disord.* **2008**, *23*, 2344–8.
(406) Rakovic, A.; Stiller, B.; Djarmati, A.; Flaquer, A.; Freudenberg, J.; Toliat, M. R.; Linnebank, M.; Kostic, V.; Lohmann, K.; Paus, S.; Nurnberg, P.; Kubisch, C.; Klein, C.; Wullner, U.; Ramirez, A. *Mov. Disord.* **2008**, *24*, 429–433.
(407) Ramirez, A.; Heimbach, A.; Grundemann, J.; Stiller, B.; Hampshire, D.; Cid, L. P.; Goebel, I.; Mubaidin, A. F.; Wriekat, A. L.; Roeper, J.; Al-Din, A.; Hillmer, A. M.; Karsak, M.; Liss, B.; Woods, C. G.; Behrens, M. I.; Kubisch, C. *Nat. Genet.* **2006**, *38*, 1184–91.
(408) Schultheis, P. J.; Hagen, T. T.; O'Toole, K. K.; Tachibana, A.; Burke, C. R.; McGill, D. L.; Okunade, G. W.; Shull, G. E. *Biochem. Biophys. Res. Commun.* **2004**, *323*, 731–8.
(409) Lautier, C.; Goldwurm, S.; Durr, A.; Giovannone, B.; Tsiaras, W. G.; Pezzoli, G.; Brice, A.; Smith, R. J. *Am. J. Hum. Genet.* **2008**, *82*, 822–33.
(410) Prestel, J.; Sharma, M.; Leitner, P.; Zimprich, A.; Vaughan, J. R.; Durr, A.; Bonifati, V.; De Michele, G.; Hanagasi, H. A.; Farrer, M.; Hofer, A.; Asmus, F.; Volpe, G.; Meco, G.; Brice, A.; Wood, N. W.; Muller-Myhsok, B.; Gasser, T. *Eur. J. Hum. Genet.* **2005**, *13*, 193–7.
(411) Zimprich, A.; Schulte, C.; Reinthaler, E.; Haubenberger, D.; Balzar, J.; Lichtner, P.; El Tawil, S.; Edris, S.; Foki, T.; Pirker, W.; Katzenschlager, R.; Daniel, G.; Brucke, T.; Auff, E.; Gasser, T. Parkinsonism Relat. Disord., in press.
(412) Sutherland, G. T.; Siebert, G. A.; Newman, J. R.; Silburn, P. A.; Boyle, R. S.; O'Sullivan, J. D.; Mellick, G. D. *Mov. Disord.* **2009**, *24*, 449–52.
(413) Bogaerts, V.; Engelborghs, S.; Kumar-Singh, S.; Goossens, D.; Pickut, B.; van der Zee, J.; Sleegers, K.; Peeters, K.; Martin, J. J.; Del-Favero, J.; Gasser, T.; Dickson, D. W.; Wszolek, Z. K.; De Deyn, P. P.; Theuns, J.; Van Broeckhoven, C. *Brain* **2007**, *130*, 2277–91.
(414) Gonzalez-Perez, A.; Gayan, J.; Marin, J.; Galan, J. J.; Saez, M. E.; Real, L. M.; Antunez, C.; Ruiz, A. Neurogenetics, in press.
(415) Santos, P. M.; Simoes, T.; Sa-Correia, I. *Proteomics* **2009**, *9*, 657–70.
(416) Sharma, N.; Brandis, K. A.; Herrera, S. K.; Johnson, B. E.; Vaidya, T.; Shrestha, R.; Debburman, S. K. *J. Mol. Neurosci.* **2006**, *28*, 161–78.
(417) Tanaka, M.; Kim, Y. M.; Lee, G.; Junn, E.; Iwatsubo, T.; Mouradian, M. M. *J. Biol. Chem.* **2004**, *279*, 4625–31.
(418) Klucken, J.; Shin, Y.; Masliah, E.; Hyman, B. T.; McLean, P. J. *J. Biol. Chem.* **2004**, *279*, 25497–502.
(419) Auluck, P. K.; Chan, H. Y.; Trojanowski, J. Q.; Lee, V. M.; Bonini, N. M. *Science* **2002**, *295*, 865–8.
(420) Bruening, W.; Roy, J.; Giasson, B.; Figlewicz, D. A.; Mushynski, W. E.; Durham, H. D. *J. Neurochem.* **1999**, *72*, 693–9.
(421) Xu, L.; Voloboueva, L. A.; Ouyang, Y.; Emery, J. F.; Giffard, R. G. *J. Cereb. Blood Flow Metab.* **2009**, *29*, 365–74.
(422) Mosser, D. D.; Ho, S.; Glover, J. R. *Biochemistry* **2004**, *43*, 8107–15.
(423) Shin, Y.; Klucken, J.; Patterson, C.; Hyman, B. T.; McLean, P. J. *J. Biol. Chem.* **2005**, *280*, 23727–34.
(424) Sahara, N.; Murayama, M.; Mizoroki, T.; Urushitani, M.; Imai, Y.; Takahashi, R.; Murata, S.; Tanaka, K.; Takashima, A. *J. Neurochem.* **2005**, *94*, 1254–63.
(425) Amin, V.; Cumming, D. V.; Latchman, D. S. *Neurosci. Lett.* **1996**, *206*, 45–8.
(426) Mailhos, C.; Howard, M. K.; Latchman, D. S. *J. Neurochem.* **1994**, *63*, 1787–95.
(427) Wyatt, S.; Mailhos, C.; Latchman, D. S. *Brain Res. Mol. Brain Res.* **1996**, *39*, 52–6.
(428) Guo, Z.; Lee, J.; Lane, M.; Mattson, M. *J. Neurochem.* **2001**, *79*, 361–70.
(429) Lee, M. W.; Park, S. C.; Chae, H. S.; Bach, J. H.; Lee, H. J.; Lee, S. H.; Kang, Y. K.; Kim, K. Y.; Lee, W. B.; Kim, S. S. *Biochem. Biophys. Res. Commun.* **2001**, *284*, 261–7.
(430) Kalmar, B.; Burnstock, G.; Vrbova, G.; Urbanics, R.; Csermely, P.; Greensmith, L. *Exp. Neurol.* **2002**, *176*, 87–97.
(431) Veereshwarayya, V.; Kumar, P.; Rosen, K. M.; Mestril, R.; Querfurth, H. W. *J. Biol. Chem.* **2006**, *281*, 29468–78.
(432) Salehi, A. H.; Morris, S. J.; Ho, W. C.; Dickson, K. M.; Doucet, G.; Milutinovic, S.; Durkin, J.; Gillard, J. W.; Barker, P. A. *Chem. Biol.* **2006**, *13*, 213–23.
(433) Sahara, N.; Maeda, S.; Yoshiike, Y.; Mizoroki, T.; Yamashita, S.; Murayama, M.; Park, J. M.; Saito, Y.; Murayama, S.; Takashima, A. *J. Neurosci. Res.* **2007**, *85*, 3098–108.
(434) Fukuda, T.; Shimizu, J.; Furuhata, H.; Abe, T.; Shimizu, K.; Oishi, T.; Ogihara, M.; Kubota, J.; Sasaki, A.; Sasaki, K.; Azuma, T.; Umemura, S. *Acta Neuropathol.* **2005**, *110*, 145–50.
(435) Pountney, D. L.; Raftery, M. J.; Chegini, F.; Blumbergs, P. C.; Gai, W. P. *Acta Neuropathol.* **2008**, *116*, 603–14.
(436) Uryu, K.; Richter-Landsberg, C.; Welch, W.; Sun, E.; Goldbaum, O.; Norris, E. H.; Pham, C. T.; Yazawa, I.; Hilburger, K.; Micsenyi, M.; Giasson, B. I.; Bonini, N. M.; Lee, V. M.; Trojanowski, J. Q. *Am. J. Pathol.* **2006**, *168*, 947–61.
(437) Huang, T. Y.; Minamide, L. S.; Bamburg, J. R.; Bokoch, G. M. *Dev. Cell* **2008**, *15*, 691–703.
(438) Luo, S.; Zhang, B.; Dong, X. P.; Tao, Y.; Ting, A.; Zhou, Z.; Meixiong, J.; Luo, J.; Chiu, F. C.; Xiong, W. C.; Mei, L. *Neuron* **2008**, *60*, 97–110.
(439) Waza, M.; Adachi, H.; Katsuno, M.; Minamiyama, M.; Sang, C.; Tanaka, F.; Inukai, A.; Doyu, M.; Sobue, G. *Nat. Med.* **2005**, *11*, 1088–95.

(440) Katsuno, M.; Sang, C.; Adachi, H.; Minamiyama, M.; Waza, M.; Tanaka, F.; Doyu, M.; Sobue, G. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 16801–6.
(441) Waza, M.; Adachi, H.; Katsuno, M.; Minamiyama, M.; Tanaka, F.; Doyu, M.; Sobue, G. *J. Mol. Med. (Berlin, Germany)* **2006**, *84*, 635–46.
(442) Ansar, S.; Burlison, J. A.; Hadden, M. K.; Yu, X. M.; Desino, K. E.; Bean, J.; Neckers, L.; Audus, K. L.; Michaelis, M. L.; Blagg, B. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1984–90.
(443) Lu, A.; Ran, R.; Parmentier-Batteur, S.; Nee, A.; Sharp, F. R. *J. Neurochem.* **2002**, *81*, 355–64.
(444) Shen, H. Y.; He, J. C.; Wang, Y.; Huang, Q. Y.; Chen, J. F. *J. Biol. Chem.* **2005**, *280*, 39962–9.
(445) Jeon, G. S.; Park, S. W.; Kim, D. W.; Seo, J. H.; Cho, J.; Lim, S. Y.; Kim, S. D.; Cho, S. S. *Glia* **2004**, *48*, 250–8.
(446) Birnby, D. A.; Link, E. M.; Vowels, J. J.; Tian, H.; Colacurcio, P. L.; Thomas, J. H. *Genetics* **2000**, *155*, 85–104.
(447) Murakami, M.; Koga, M.; Ohshima, Y. *Mech. Dev.* **2001**, *109*, 27–35.
(448) Singh, V.; Aballay, A. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 13092–7.
(449) Finch, C. E.; Ruvkun, G. *Annu. Rev. Genomics Hum. Genet.* **2001**, *2*, 435–62.
(450) Mohri-Shiomi, A.; Garsin, D. A. *J. Biol. Chem.* **2008**, *283*, 194–201.
(451) Blackinton, J.; Ahmad, R.; Miller, D. W.; van der Brug, M. P.; Canet-Aviles, R. M.; Hague, S. M.; Kaleem, M.; Cookson, M. R. *Brain Res. Mol. Brain Res.* **2005**, *134*, 76–83.
(452) Moore, D. J.; Zhang, L.; Troncoso, J.; Lee, M. K.; Hattori, N.; Mizuno, Y.; Dawson, T. M.; Dawson, V. L. *Hum. Mol. Genet.* **2005**, *14*, 71–84.
(453) Ko, H. S.; Bailey, R.; Smith, W. W.; Liu, Z.; Shin, J. H.; Lee, Y. I.; Zhang, Y. J.; Jiang, H.; Ross, C. A.; Moore, D. J.; Patterson, C.; Petrucelli, L.; Dawson, T. M.; Dawson, V. L. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 2897–902.
(454) Wang, L.; Xie, C.; Greggio, E.; Parisiadou, L.; Shim, H.; Sun, L.; Chandran, J.; Lin, X.; Lai, C.; Yang, W. J.; Moore, D. J.; Dawson, T. M.; Dawson, V. L.; Chiosis, G.; Cookson, M. R.; Cai, H. *J. Neurosci.* **2008**, *28*, 3384–91.
(455) Hurtado-Lorenzo, A.; Anand, V. S. *J. Neurosci.* **2008**, *28*, 6757–9.
(456) Poirier, J.; Donaldson, J.; Barbeau, A. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 25–33.
(457) Baek, S. Y.; Lee, M. J.; Jung, H. S.; Kim, H. J.; Lee, C. R.; Yoo, C.; Lee, J. H.; Lee, H.; Yoon, C. S.; Kim, Y. H.; Park, J.; Kim, J. W.; Jeon, B. S.; Kim, Y. *Neurotoxicology* **2003**, *24*, 657–65.
(458) Baek, S. Y.; Kim, Y. H.; Oh, S. O.; Lee, C. R.; Yoo, C. I.; Lee, J. H.; Lee, H.; Sim, C. S.; Park, J.; Kim, J. W.; Yoon, C. S.; Kim, Y. *Hum. Exp. Toxicol.* **2007**, *26*, 203–11.
(459) Strozyk, D.; Launer, L. J.; Adlard, P. A.; Cherny, R. A.; Tsatsanis, A.; Volitakis, I.; Blennow, K.; Petrovitch, H.; White, L. R.; Bush, A. I. Neurobiol. Aging, in press.
(460) Cawte, J.; Kilburn, C.; Florence, M. *Neurotoxicology* **1989**, *10*, 263–70.
(461) Sitburana, O.; Ondo, W. G. *Parkinsonism Relat. Disord.* **2009**, *15*, 165–74.

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