We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



1

Etiology and Pathogenesis of Parkinson's Disease

Taku Hatano and Nobutaka Hattori
Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan

1. Introduction

The pathological hallmarks of Parkinson's disease (PD) are marked loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), which causes dopamine depletion in the striatum, and the presence of intracytoplasmic inclusions known as Lewy bodies in the remaining cells. It remains unclear why dopaminergic neuronal cell death and Lewy body formation occur in PD. The pathological changes in PD are seen not only in the SNc but also in the locus coeruleus, pedunculo pontine nucleus, raphe nucleus, dorsal motor nucleus of the vagal nerve, olfactory bulb, parasympathetic as well as sympathetic post-ganglionic neurons, Mynert nucleus, and the cerebral cortex (Braak et al. 2003). Widespread neuropathology in the brainstem and cortical regions are responsible for various motor and non-motor symptoms of PD. Although dopamine replacement therapy improves the functional prognosis of PD, there is currently no treatment that prevents the progression of this disease.

Previous studies provided possible evidence that the pathogenesis of PD involves complex interactions between environmental and multiple genetic factors. Exposure to the environmental toxin MPTP was identified as one cause of parkinsonism in 1983 (Langston & Ballard 1983). In addition to MPTP, other environmental toxins, such as the herbicide paraquat and the pesticide rotenone have been shown to contribute to dopaminergic neuronal cell loss and parkinsonism. In contrast, cigarette smoking, caffeine use, and high normal plasma urate levels are associated with lower risk of PD (Hernan et al. 2002). Recently, Braak and coworkers proposed the "Dual Hit" theory, which postulated an unknown pathogen accesses the brain through two pathways, the nose and the gut (Hawkes et al. 2007). Subsequently, a prion-like mechanism might contribute to the propagation of α-synuclein from the peripheral nerve to the central nervous system (Angot et al. 2010).

Approximately 5% of patients with clinical features of PD have clear familial etiology. Therefore, genetic factors clearly contribute to the pathogenesis of PD. Over the decade, more than 16 loci and 11 causative genes have been identified, and many studies have shed light on their implication in, not only monogenic, but also sporadic forms of PD. Recent studies revealed that PD-associated genes play important roles in cellular functions, such as mitochondrial functions, the ubiquitin-proteasomal system, autophagy-lysosomal pathway, and membrane trafficking (Hatano et al. 2009). In this chapter, we review the investigations of environmental and genetic factors of PD (Figure 1).

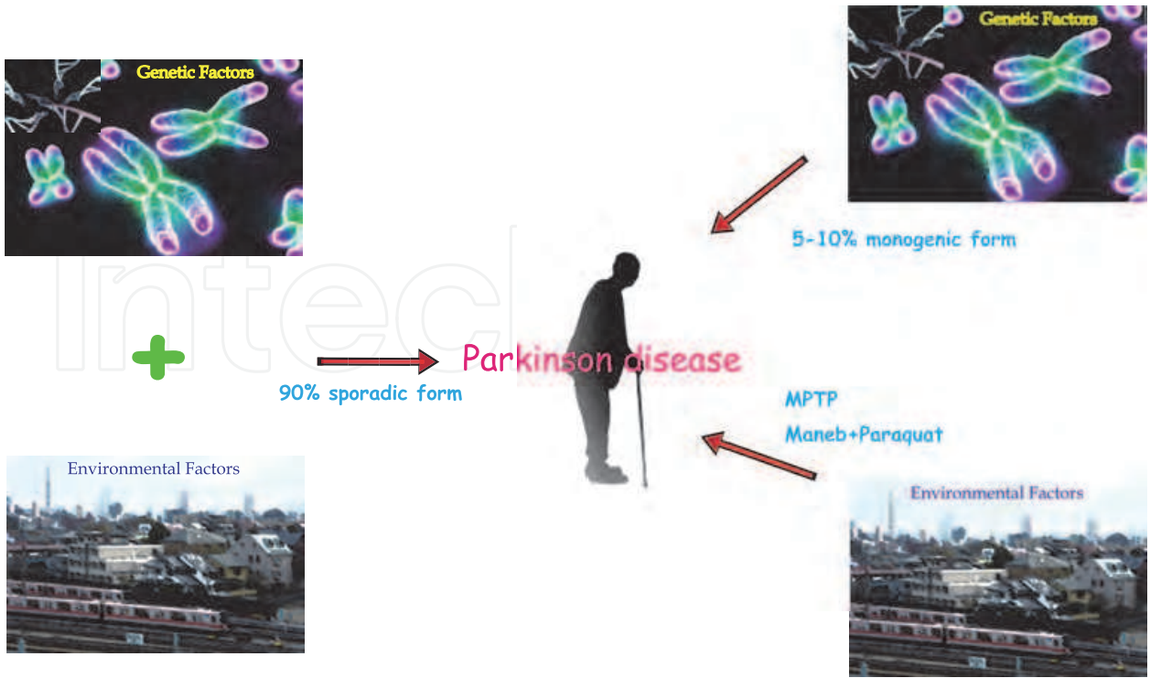


Fig. 1. Although the etiology of Parkinson disease (PD) remains unknown, 5-10% of patients have clear familial etiology, which show a classical recessive or dominant Mendelian mode of inheritance. On the other hand, MPTP or a combination of maneb and paraquat are environmental risk factors for PD. Several PD-related genetic factors (e.g., SNPs in α-synuclein) have been discovered, and the interaction between genetic and environmental factors might contribute to sporadic PD.

2. Environmental factors and PD

2.1 1-methyl-4phenyl-1,2,3,6-tetrahydro-pyridine (MPTP)

Langston et al reported on four patients who developed typical parkinsonism after repeated injection of MPTP intravenously (Langston & Ballard 1983). Furthermore, these patients responded to treatment with levodopa and bromocriptine and experienced motor fluctuations, similar to patients with idiopathic PD. Interestingly, fluorodopa positron emission tomography (FD-PET) study of subjects exposed to MPTP demonstrated that transient exposure to this toxin could lead to progressive nigral degeneration (Vingerhoets et al. 1994). Neuropathological findings of 3 subjects with MPTP-induced parkinsonism showed moderate to severe dopaminergic neuronal degeneration without Lewy bodies in the substantia nigra. Interestingly, there was gliosis; clustering microglia around nerve cells and extraneural melanin. These findings indicated active and continuing neuronal cell degeneration (Langston et al. 1999). PET and neuropathological studies suggested that an active neuronal cell death process was persistent for years after these subjects were exposed to MPTP. MPTP is a by-product of the chemical synthesis of a narcotic meperidine analog. This chemical agent is highly lypophilic, therefore it quickly crosses the blood-brain barrier and converts to 1-methyl-4-phenyl-2,3-dihydropyridinium ion (MPP+), which is the active toxic compound, via monoamine oxidase B within nondopaminergic cells, such as glial cells and serotonergic neurons. MPP+ is transported into dopamine neurons by the dopamine

transporter, and therefore exhibits selective toxicity to dopaminergic neurons. Furthermore, MPP+ accumulates in mitochondria, where it inhibits the mitochondrial electron transport chain component complex I (Przedborski & Vila 2003). Mizuno et al reported that MPP+ inhibited the α-ketoglutarate dehydrogenase complex of the mitochondrial tricarboxylic acid cycle, which synthesizes succinate from α–ketoglutarate (Mizuno et al. 1987). In SNc of sporadic PD subjects, decreased activity and protein levels of complex I have also been reported (Schapira et al. 1989). Thus biochemical changes in dopaminergic neuronal degeneration in sporadic PD were essentially similar to those of subjects exposed to MPTP.

2.2 Pesticides

Epidemiological studies have suggested the association between PD and exposure of pesticides such as rotenone and paraquat. Rotenone is a potent and high-affinity specific inhibitor of complex I. In rodents, continuous infusion of these toxic agents induced dopaminergic neuronal cell death and inclusion bodies, which were similar to Lewy bodies in PD patients (Betarbet et al. 2000). Therefore, both MPTP and rotenone disrupt mitochondrial function and play important roles in the nigral cell degeneration in PD.

Paraquat, which is a member of a chemical class known as bipyridyl derivatives, is one of the most commonly used pesticides, and leads to oxidative and nitrative stress (Berry et al.). The chemical structure of paraquat is similar to MPP+. Epidemiologic studies implicate the association between exposure to this toxin and the development of PD. Interestingly, recent studies revealed that exposure to a combination of paraquat and maneb, which is also widely used as an agricultural pesticide, exacerbate dopaminergic degeneration in the rodent model and cause an increased incidence of PD in humans (Costello et al. 2009). In this context, exposure to a combination of several toxins could lead to greater risk of developing PD than a single toxin.

2.3 Caffeine, cigarette

Smokers and coffee drinkers have been associated with a lower risk of PD in several epidemiological studies. Hernan et al. conducted a meta-analytic review for the association between caffeine intake, smoking, and the risk of PD. Interestingly the cigarette smokers had 60% lower risk for the development of PD than people without a history of smoking (Hernan et al. 2002). Some experiments suggested that chronic nicotine treatment could have protective effects against the nigrostriatal neuronal cell death in MPTP-treated animal models. Several studies revealed that cigarette smoking inhibited monoamine oxidase (MAO) activity and nicotine stimulated dopamine release. As a result, cigarette smoking may suppress free radical generation via MAO-B-associated metabolism of dopamine, and be able to protect against dopaminergic cell death (Miller et al. 2007). Similar to cigarette smoking, coffee drinking could result in a 30% decreased risk of PD compared with non-coffee drinkers (Hernan et al. 2002). Chen et al reported that caffeine had similar effects as A_{2A} antagonists, and attenuated MPTP toxicity via A_{2A} receptor blockade (Chen et al. 2001).

2.4 Disease process and dual hit theory

Braak and colleagues proposed neuropathological staging in PD. They reported that the dorsal motor nucleus of the glossopharyngeal and vagal nerves and the anterior olfactory nucleus were initially affected, and subsequently the substantia nigra and locus coeruleus

became involved. Cortical areas showed less vulnerability, gradually becoming affected (Braak et al. 2003). These pathological findings suggest that the neuronal degeneration in PD may extend from peripheral systems, such as olfactory and autonomic systems to cortices. They also proposed the so-called "Dual-Hit" hypothesis, which suggests that neurotropic pathogens may enter the nervous system via both nasal and intestinal epithelium (Hawkes et al. 2007). These events may promote α-synuclein aggregation and subsequently misfolded α-synuclein may propagate between cells in a prion-like manner (Angot et al. 2010). By using cultured cell models and α-synuclein transgenic mice models, Desplats et al demonstrated direct neuron to neuron transmission of α-synuclein aggregates (Desplats et al. 2009). Actually, in the brains of PD patients who received fetal ventral mesencephalic transplants, grafted nigral neurons contained Lewy body-like inclusions (Li et al. 2008, Kordower et al. 2008). These results corroborate the hypothesis that progression of α-synuclein aggregation relies on the same mechanisms of prion propagation. In conclusion, environmental factors could play important roles in the pathomechanisms of neuronal degeneration in sporadic PD

3. Genetic factors and PD

3.1 α-synuclein

α-synuclein is a 140-amino acid protein that is abundantly expressed throughout the brain, and especially in presynaptic nerve terminals. In 1997, an α-synuclein A53T mutation was isolated from an autosomal dominant PD case. Cases of sporadic PD and A53T-associated patients displayed similar clinical phenotypes, with the exception of a relatively earlier age of onset and atypical features such as cognitive decline, severe central hypoventilation, orthostatic hypotension, myoclonus and urinary incontinence (Polymeropoulos et al. 1997, Spira et al. 2001). In addition, A30P (Kruger et al. 1998) and E46K (Zarranz et al. 2004) mutations were also identified. Following the identification of mutations in the α-synuclein gene, multiplication of *SNCA* has also been identified to cause autosomal dominant familial PD (Ibanez et al. 2004, Chartier-Harlin et al. 2004, Nishioka et al. 2006, Ahn et al. 2008). Considering that α-synuclein protein is the major component of Lewy bodies (Spillantini et al. 1997), aggregation of α-synuclein is thought to be a key event in dopaminergic neuronal cell death in both *SNCA*-linked and sporadic PD (Lee & Trojanowski 2006). α-synuclein has a high propensity to aggregate, just like other proteins associated with neurodegenerative disease, such as tau, amyloid precursor protein, and poly Q proteins (Bossy-Wetzel et al. 2004, Cookson 2005). α-synuclein exists in solution as an unstructured monomer, however, monomeric α-synuclein can form insoluble fibrillar aggregates with an antiparallel β-sheet structure through the formation of oligomeric forms (protofibrils). The fibrils assemble in vitro, and these filaments closely aggregate just like pathologic inclusions in PD or MSA (Cookson 2005). Fibril formation by pathogenic mutations is accelerated in vitro compared with the wild type (Narhi et al. 1999, Conway et al. 2000, Greenbaum et al. 2005). In several experimental models, including cultured cells, rodent, *Drosophilae* and *Caenorhabditis elegans*, pathogenic mutants also promote self-aggregation and oligomerization into protofibrils, compared with the wild-type protein. Some studies suggest that α-synuclein could participate in a protein degradation pathway such as the ubiquitin-proteasomal system (UPS) (Rideout et al. 2001, Zhang et al. 2008), and chaperone-mediated autophagy(Cuervo et al. 2004).

The functions of α-synuclein under normal physiological conditions remain unknown. However, several studies have shown that α-synuclein associates with synaptic vesicles and modulates neurotransmitter release (Jensen et al. 1998, Li et al. 2004). Electrophysiological study in α-synuclein knockout mice revealed that α-synuclein could act as an activity-negative regulator of DA neurotransmission at synaptic terminals (Abeliovich et al. 2000). α-synuclein is also speculated to have various other functions, such as modulation of tyrosine hydroxylase (TH) activation (Perez et al. 2002), inhibition of vesicular monoamine transporter-2 (VMAT2) activity (Guo et al. 2008), and interaction with septin4, which have been implicated in exocytosis (Ihara et al. 2007). Recently, Cooper and colleagues reported that α-synuclein blocked endoplasmic reticulum (ER)-to-Golgi vesicular trafficking, and induced ER stress followed by cell death (Cooper et al. 2006). In addition, α-synuclein may interact with the synaptic membrane through lipid rafts (Fortin et al. 2004, Kubo et al. 2005), which are known to be a signaling platform for cellular functions such as signal transduction, membrane trafficking and cytoskeletal organization. These data indicate that α-synuclein plays important roles in vesicle sorting and regulation of catecholamine metabolism in dopaminergic neurons.

3.2 LRRK2

LRRK2 mutations were identified as the causative gene for PARK8-linked familial PD (Paisan-Ruiz et al. 2004), (Zimprich et al. 2004). Some screening studies reported that *LRRK2* mutations were identified not only in familial PD but also in sporadic PD. Since then, *LRRK2* mutations seem to be the most frequent cause of autosomal dominantly-inherited familial PD (Lesage et al. 2006, Ozelius et al. 2006). R1628P and G2385R are polymorphic mutations and have been demonstrated as risk factors for sporadic PD in Asian populations (Di Fonzo et al. 2006, Funayama et al. 2007). The clinical features of patients with *LRRK2* mutations essentially resemble sporadic PD with good response to levodopa. Pathological studies of autopsy cases with I1371V, A1441C, Y1699C, G2019S, and I2020T mutations have revealed neuronal cell loss accompanied by Lewy bodies indistinguishable from those of sporadic PD. Some individuals display pleomorphic pathologies, including synucleinopathy, tauopathy, TDP-43 proteinopathy, substantia nigral neuronal loss alone, and neuronal loss with nuclear ubiquitin inclusions (Zimprich et al. 2004, Covy et al. 2009). Although some antibodies against the functional domain fail to detect Lewy bodies, other antibodies directed against the N-terminal and C-terminal residues are able to stain Lewy bodies. Thus, there is controversy as to whether LRRK2 is a component of Lewy bodies. LRRK2 also colocalizes with tau-positive inclusions in fronto-temporal dementia with MAPT N279K mutation (Miklossy et al. 2007). Considering this pleomorphic pathology, LRRK2 seems to be involved in disease-modifying pathways in various neurodegenerative diseases.

The LRRK2 protein is a 2527 amino acid polypeptide (~280 kDa), consisting of leucine-rich repeats (LRR), Ras of complex proteins (Roc) followed by the C-terminal of Roc (COR), mitogen-activated protein kinase kinase kinase (MAPKKK) and WD40 domains (Mata et al. 2006). LRRK2 protein belongs to the ROCO protein family. LRRK2 proteins localize in the cytoplasm and membranous organelles, including ER, Golgi apparatus, early endosomes, lysosomes, synaptic vesicles, mitochondria, and the plasma membrane (Hatano et al. 2007). We found LRRK2 bound to lipid rafts within the synaptosomes (Hatano et al. 2007). Several results suggest that LRRK2 also interacts with the Rab family and presynaptic proteins, and modulates the membrane trafficking system.

An in vitro phosphorylation assay using thin-layer chromatography revealed that LRRK2 might also function as a serine/threonine kinase (West et al. 2007). The frequent LRRK2 G2019S and adjacent I2020T mutations are located within the kinase domain and exhibit increased activity (West et al. 2005, Gloeckner et al. 2006). The kinase activity could be regulated by GTP via the intrinsic GTPase Roc domain (Smith et al. 2006, West et al. 2007). Considering that at least some of the mutations alter the kinase activity and are neurotoxic, misregulated kinase activity may explain the core damaging effect of LRRK2 in neurons. Actually, several groups reported that LRKK2 is able to modulate several signal transduction pathways, such as the ERK1/2, TNFα/FasL and Wnt signaling pathways (Berwick & Harvey 2011), and the microRNA pathway, which regulates protein synthesis (Gehrke et al. 2010). The interaction between LRRK2 and parkin is also reported, but there is no evidence to associate LRRK2 with other genes, such as α-synuclein, tau, and DJ-1 (Smith et al. 2005). Further investigations may reveal how LRRK2 participates in pathways of other PARK gene-related dopaminergic neuronal degeneration.

3.3 PINK1/Parkin pathway

Mutations in parkin were identified as the cause of autosomal recessive early onset PD (EOPD) (Kitada et al. 1998), followed by mutations in DJ-1 (Bonifati et al. 2003), and PINK1 (Valente et al. 2004, Hatano et al. 2004). PARK2-linked EOPD is characterized by a spontaneous improvement after sleep or a nap, diurnal fluctuation, some dystonic features which are predominantly in the foot, good response to levodopa, early onset (average age of onset is in the twenties), no dementia, no autonomic failure, and lack of Lewy bodies (Yamamura et al. 1973, Mori et al. 1998). The clinical features of PARK2-linked EOPD are distinguishable from those of patients with the common form of PD. Pathological studies in patients with PARK2-linked EOPD have shown that the substantia nigra and locus coeruleus exhibit selective degeneration with gliosis (Mori et al. 1998). Other pigmented neurons in these regions contain traces of melanin pigments, and the cell cytoplasm is scanty compared with that of normal individuals without neurodegenerative disorders. Although the brain tissue of two cases, which were positive for parkin mutation showed the presence of Lewy bodies (Farrer et al. 2001, Pramstaller et al. 2005), they are generally absent in PARK2-mutation brains.

Parkin protein is linked to the ubiquitin-proteasome pathway as a ubiquitin ligase (E3) (Shimura et al. 2000). Most Lewy bodies also stain strongly for ubiquitin, which is highly involved in the protein degradation system. Furthermore, the collaboration between parkin and PINK1 could be associated with mitochondrial quality control systems (Geisler et al. 2010, Vives-Bauza et al. 2010, Narendra et al. 2010, Kawajiri et al. 2010, Matsuda et al. 2010). *Parkin*-deficient *Drosophila* exhibit mitochondrial structural alterations in testes and muscle tissue (Greene et al. 2003). *PINK1*-deficient *Drosophila* also exhibited degeneration of flight muscles and dopaminergic neuronal cells accompanied by mitochondrial abnormality, and share phenotypic similarity with *parkin*-deficient *Drosophila*. Overexpression of parkin reversed the muscle damage in *PINK1*-deficient *Drosophila*, but PINK1 overexpression could not reverse the *parkin*-null-linked damage (Clark et al. 2006, Park et al. 2006). Furthermore, mitochondrial abnormalities in *PINK1*- or *parkin*-deficient *Drosophila* were reversed by knockdown of *Mitofusin* (*Mfn*), *Optic atrophy 1* (*Opa1*), or overexpression of Dynamin-related protein1 (Drp1), which participate in mitochondrial fusion and fission (Deng et al. 2008). These findings suggest that PINK1 might associate upstream of parkin to regulate

mitochondrial dynamics. The interaction between PINK1 and parkin was also analyzed by using a cultured cell system (Shiba et al. 2009). Narendra and colleagues (2010) reported accumulation of parkin in mitochondria impaired by carbonyl cyanide m-chlorophenylhydrazone. Such accumulation promotes the selective autophagy of damaged mitochondria (mitophagy). Several groups have recently shown that PINK1 might be required for parkin-mediated mitophagy (Geisler et al. 2010; Vives-Bauza et al. 2010; Narendra et al. 2010; Kawajiri et al. 2010; Matsuda et al. 2010). We reported that parkin relocates cytoplasm to damaged mitochondria in a membrane potential-dependent manner (Matsuda et al.2010). PINK1 plays a critical role in recruiting parkin to mitochondria with low membrane potential to initiate the autophagic degradation of damaged mitochondria. Pathogenic parkin mutations affect mitochondrial localization. Therefore, loss of the association between parkin and damaged mitochondria could lead to nigral cell death in *PARK2-linked* EOPD. Immunoprecipitation using anti-LC3 antibodies revealed the direct interaction between PINK1 and endogenous LC3 (Kawajiri et al. 2010). These results suggest that mitochondrial degradation by the PINK1/Parkin pathway is dependent on mitochondrial autophagic activity. Geisler et al. (2010) also reported that the kinase activity of PINK1 in mitochondria might be needed to induce translocation of parkin to depolarized mitochondria. Parkin modified VDAC1 via Lys27 poly-ubiquitylation, and promoted autophagic degradation of damaged mitochondria. Interestingly, they also revealed that the autophagic adaptor p62/SQSTM1 is recruited to mitochondrial clusters and could be associated with PINK1/Parkin-mediated mitophagy. Funayama et al. identified PD patients carrying both *parkin* and *PINK1* mutations, whose onset age was younger than that of patients with the same *parkin* mutation alone. The presence of digenic mutations, such as *parkin* plus *PINK1* mutations, suggests that a *PINK1* mutation could influence the clinical symptoms of parkin-linked PD (Funayama et al. 2008). However, Kitada and colleagues (Kitada et al. 2009) reported that triple knockout of Parkin, PINK1, and DJ-1 resulted in normal morphology and numbers of dopaminergic and noradrenergic neurons in the substantia nigra and locus coeruleus. Therefore, understanding the PINK1/Parkin pathway underlying the mitochondrial dynamics helps clarify the pathomechanics in PD.

4. Conclusion

The pathological mechanisms and causes of PD remain largely unknown. Most PD patients have not been associated with a particular genetic background or certain exposure of environmental toxins. However, Japanese and European groups performed genome-wide association studies and revealed that the α-synuclein locus, the MAPT locus, the LRRK2 locus, the BST1 locus, and 1q32 (PARK16) may be genetic risk factors for PD (Satake et al. 2009, Simon-Sanchez et al. 2009). Although the α-synuclein locus, LRRK2 locus, and PARK16 are confirmed as genetic risk factors for PD across populations, BST1 and MAPT may be risk loci correlated with ethnic differences. Conversely, α-synuclein is involved in the virulent effects of the environmental toxin MPTP. High mRNA and protein levels of α-synuclein have been described in the brains of MPTP-treated mice (Vila et al. 2000). Although α-synuclein-deficient mice exhibited marked resistance to MPTP-induced degeneration of dopamine neurons (Dauer et al. 2002), some lines of α-synuclein transgenic mice have exhibited increased sensitivity to MPTP (Nieto et al. 2006, Yu et al. 2008). These results also suggest that various genetic-environmental interactions may have influences on dopaminergic neuronal metabolism and kinetics, such as signal transduction, vesicle

transport, autophagy (mitophagy), and mitochondrial stress (Figure 2). In addition, a prion-like transmission of α-synuclein may trigger the development of nigral degeneration in PD. Taken together, the new findings based on the interaction between familial PD-related proteins and environmental factors could shed light on the pathomechanisms for PD.

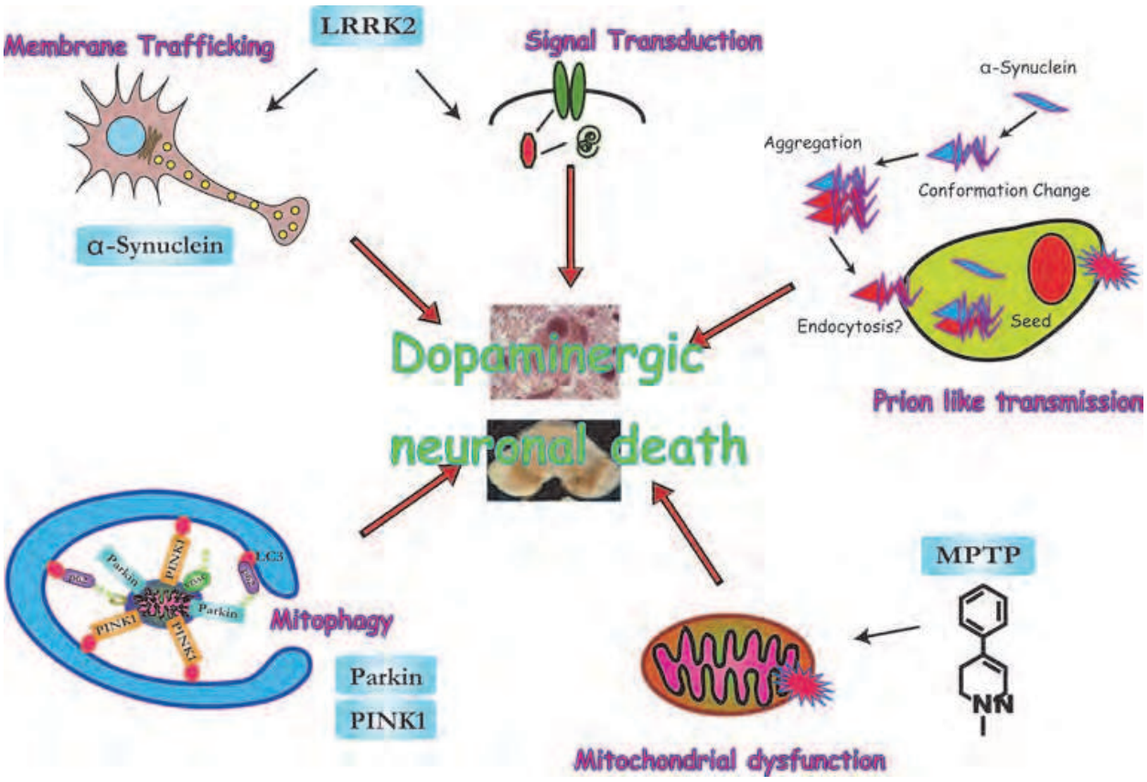


Fig. 2. Summary of pathogenetic factors involved in Parkinson's disease (PD). Recent evidence indicated that the PINK1/Parkin pathway participates in mitochondrial removal via autophagy (mitophagy). LRRK2 may associate with cell signaling pathways and the membrane trafficking system. Several environmental factors, such as MPTP, paraquat, and rotenone are known as mitochondrial toxins. In addition, a prion-like transmission of α-synuclein may trigger the development of nigral degeneration in PD.

5. Acknowledgments

This study was supported in part by grants for research on diseases of the brain from the Ministry of Education, Science and Sports in Japan.

6. References

Abeliovich, A., Schmitz, Y., Farinas, I. et al. (2000) Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron,* 25, 239-252.

Ahn, T. B., Kim, S. Y., Kim, J. Y. et al. (2008) alpha-Synuclein gene duplication is present in sporadic Parkinson disease. *Neurology,* 70, 43-49.

Angot, E., Steiner, J. A., Hansen, C., Li, J. Y. and Brundin, P. (2010) Are synucleinopathies prion-like disorders? *Lancet Neurol,* 9, 1128-1138.

Berry, C., La Vecchia, C. and Nicotera, P. (2010) Paraquat and Parkinson's disease. *Cell Death Differ,* 17, 1115-1125.

Berwick, D. C. and Harvey, K. (2011) LRRK2 signaling pathways: the key to unlocking neurodegeneration? *Trends Cell Biol*, 21, 254-265.

Betarbet, R., Sherer, T. B., MacKenzie, G., Garcia-Osuna, M., Panov, A. V. and Greenamyre, J. T. (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci,* 3, 1301-1306.

Bonifati, V., Rizzu, P., van Baren, M. J. et al. (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science,* 299, 256-259.

Bossy-Wetzel, E., Schwarzenbacher, R. and Lipton, S. A. (2004) Molecular pathways to neurodegeneration. *Nat Med,* 10 Suppl, S2-9.

Braak, H., Del Tredici, K., Rub, U., de Vos, R. A., Jansen Steur, E. N. and Braak, E. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging,* 24, 197-211.

Chartier-Harlin, M. C., Kachergus, J., Roumier, C. et al. (2004) Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet,* 364, 1167-1169.

Chen, J. F., Xu, K., Petzer, J. P. et al. (2001) Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease. *J Neurosci,* 21, RC143.

Clark, I. E., Dodson, M. W., Jiang, C., Cao, J. H., Huh, J. R., Seol, J. H., Yoo, S. J., Hay, B. A. and Guo, M. (2006) Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. *Nature,* 441, 1162-1166.

Conway, K. A., Lee, S. J., Rochet, J. C., Ding, T. T., Williamson, R. E. and Lansbury, P. T., Jr. (2000) Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. *Proc Natl Acad Sci U S A,* 97, 571-576.

Cookson, M. R. (2005) The biochemistry of Parkinson's disease. *Annu Rev Biochem,* 74, 29-52.

Cooper, A. A., Gitler, A. D., Cashikar, A. et al. (2006) Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. *Science,* 313, 324-328.

Costello, S., Cockburn, M., Bronstein, J., Zhang, X. and Ritz, B. (2009) Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am J Epidemiol,* 169, 919-926.

Covy, J. P., Yuan, W., Waxman, E. A., Hurtig, H. I., Van Deerlin, V. M. and Giasson, B. I. (2009) Clinical and pathological characteristics of patients with leucine-rich repeat kinase-2 mutations. *Mov Disord,* 24, 32-39.

Cuervo, A. M., Stefanis, L., Fredenburg, R., Lansbury, P. T. and Sulzer, D. (2004) Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. *Science,* 305, 1292-1295.

Dauer, W., Kholodilov, N., Vila, M. et al. (2002) Resistance of alpha -synuclein null mice to the parkinsonian neurotoxin MPTP. *Proc Natl Acad Sci U S A,* 99, 14524-14529.

Deng, H., Dodson, M. W., Huang, H. and Guo, M. (2008) The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in Drosophila. *Proc Natl Acad Sci U S A,* 105, 14503-14508.

Desplats, P., Lee, H. J., Bae, E. J., Patrick, C., Rockenstein, E., Crews, L., Spencer, B., Masliah, E. and Lee, S. J. (2009) Inclusion formation and neuronal cell death through neuron-

to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci U S A,* 106, 13010-13015.

Di Fonzo, A., Wu-Chou, Y. H., Lu, C. S. et al. (2006) A common missense variant in the LRRK2 gene, Gly2385Arg, associated with Parkinson's disease risk in Taiwan. *Neurogenetics,* 7, 133-138.

Farrer, M., Chan, P., Chen, R. et al. (2001) Lewy bodies and parkinsonism in families with parkin mutations. *Ann Neurol,* 50, 293-300.

Fortin, D. L., Troyer, M. D., Nakamura, K., Kubo, S., Anthony, M. D. and Edwards, R. H. (2004) Lipid rafts mediate the synaptic localization of alpha-synuclein. *J Neurosci,* 24, 6715-6723.

Funayama, M., Li, Y., Tomiyama, H. et al. (2007) Leucine-rich repeat kinase 2 G2385R variant is a risk factor for Parkinson disease in Asian population. *Neuroreport,* 18, 273-275.

Funayama, M., Li, Y., Tsoi, T. H. et al. (2008) Familial Parkinsonism with digenic parkin and PINK1 mutations. *Mov Disord,* 23, 1461-1465.

Gehrke, S., Imai, Y., Sokol, N. and Lu, B. (2010) Pathogenic LRRK2 negatively regulates microRNA-mediated translational repression. *Nature,* 466, 637-641.

Geisler, S., Holmstrom, K. M., Skujat, D., Fiesel, F. C., Rothfuss, O. C., Kahle, P. J. and Springer, W. (2010) PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat Cell Biol,* 12, 119-131.

Gloeckner, C. J., Kinkl, N., Schumacher, A., Braun, R. J., O'Neill, E., Meitinger, T., Kolch, W., Prokisch, H. and Ueffing, M. (2006) The Parkinson disease causing LRRK2 mutation I2020T is associated with increased kinase activity. *Hum Mol Genet,* 15, 223-232.

Greenbaum, E. A., Graves, C. L., Mishizen-Eberz, A. J., Lupoli, M. A., Lynch, D. R., Englander, S. W., Axelsen, P. H. and Giasson, B. I. (2005) The E46K mutation in alpha-synuclein increases amyloid fibril formation. *J Biol Chem,* 280, 7800-7807.

Greene, J. C., Whitworth, A. J., Kuo, I., Andrews, L. A., Feany, M. B. and Pallanck, L. J. (2003) Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. *Proc Natl Acad Sci U S A,* 100, 4078-4083.

Guo, J. T., Chen, A. Q., Kong, Q., Zhu, H., Ma, C. M. and Qin, C. (2008) Inhibition of vesicular monoamine transporter-2 activity in alpha-synuclein stably transfected SH-SY5Y cells. *Cell Mol Neurobiol,* 28, 35-47.

Hatano, T., Kubo, S., Imai, S., Maeda, M., Ishikawa, K., Mizuno, Y. and Hattori, N. (2007) Leucine-rich repeat kinase 2 associates with lipid rafts. *Hum Mol Genet,* 16, 678-690.

Hatano, T., Kubo, S., Sato, S. and Hattori, N. (2009) Pathogenesis of familial Parkinson's disease: new insights based on monogenic forms of Parkinson's disease. *J Neurochem,* 111, 1075-1093.

Hatano, Y., Sato, K., Elibol, B. et al. (2004) PARK6-linked autosomal recessive early-onset parkinsonism in Asian populations. *Neurology,* 63, 1482-1485.

Hawkes, C. H., Del Tredici, K. and Braak, H. (2007) Parkinson's disease: a dual-hit hypothesis. *Neuropathol Appl Neurobiol,* 33, 599-614.

Hernan, M. A., Takkouche, B., Caamano-Isorna, F. and Gestal-Otero, J. J. (2002) A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol,* 52, 276-284.

Ibanez, P., Bonnet, A. M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Durr, A. and Brice, A. (2004) Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. *Lancet,* 364, 1169-1171.

Ihara, M., Yamasaki, N., Hagiwara, A. et al. (2007) Sept4, a component of presynaptic scaffold and Lewy bodies, is required for the suppression of alpha-synuclein neurotoxicity. *Neuron,* 53, 519-533.

Jensen, P. H., Nielsen, M. S., Jakes, R., Dotti, C. G. and Goedert, M. (1998) Binding of alpha-synuclein to brain vesicles is abolished by familial Parkinson's disease mutation. *J Biol Chem,* 273, 26292-26294.

Kawajiri, S., Saiki, S., Sato, S., Sato, F., Hatano, T., Eguchi, H. and Hattori, N. (2010) PINK1 is recruited to mitochondria with parkin and associates with LC3 in mitophagy. *FEBS Lett,* 584, 1073-1079.

Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y. and Shimizu, N. (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature,* 392, 605-608.

Kitada, T., Tong, Y., Gautier, C. A. and Shen, J. (2009) Absence of nigral degeneration in aged parkin/DJ-1/PINK1 triple knockout mice. *J Neurochem,* 111, 696-702.

Kordower, J. H., Chu, Y., Hauser, R. A., Freeman, T. B. and Olanow, C. W. (2008) Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nat Med,* 14, 504-506.

Kruger, R., Kuhn, W., Muller, T. et al. (1998) Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat Genet,* 18, 106-108.

Kubo, S., Nemani, V. M., Chalkley, R. J., Anthony, M. D., Hattori, N., Mizuno, Y., Edwards, R. H. and Fortin, D. L. (2005) A combinatorial code for the interaction of alpha-synuclein with membranes. *J Biol Chem,* 280, 31664-31672.

Langston, J. W. and Ballard, P. A., Jr. (1983) Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med,* 309, 310.

Langston, J. W., Forno, L. S., Tetrud, J., Reeves, A. G., Kaplan, J. A. and Karluk, D. (1999) Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. *Ann Neurol,* 46, 598-605.

Lee, V. M. and Trojanowski, J. Q. (2006) Mechanisms of Parkinson's disease linked to pathological alpha-synuclein: new targets for drug discovery. *Neuron,* 52, 33-38.

Lesage, S., Durr, A., Tazir, M., Lohmann, E., Leutenegger, A. L., Janin, S., Pollak, P. and Brice, A. (2006) LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. *N Engl J Med,* 354, 422-423.

Li, J. Y., Englund, E., Holton, J. L. et al. (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med,* 14, 501-503.

Li, W., Hoffman, P. N., Stirling, W., Price, D. L. and Lee, M. K. (2004) Axonal transport of human alpha-synuclein slows with aging but is not affected by familial Parkinson's disease-linked mutations. *J Neurochem,* 88, 401-410.

Mata, I. F., Wedemeyer, W. J., Farrer, M. J., Taylor, J. P. and Gallo, K. A. (2006) LRRK2 in Parkinson's disease: protein domains and functional insights. *Trends Neurosci,* 29, 286-293.

Matsuda, N., Sato, S., Shiba, K. et al. (2010) PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. *J Cell Biol,* 189, 211-221.

Miklossy, J., Qing, H., Guo, J. P., Yu, S., Wszolek, Z. K., Calne, D., McGeer, E. G. and McGeer, P. L. (2007) Lrrk2 and chronic inflammation are linked to pallido-ponto-nigral degeneration caused by the N279K tau mutation. *Acta Neuropathol,* 114, 243-254.

Miller, L. R., Mukherjee, S., Ansah, T. A. and Das, S. K. (2007) Cigarette smoke and dopaminergic system. *J Biochem Mol Toxicol,* 21, 325-335.

Mizuno, Y., Saitoh, T. and Sone, N. (1987) Inhibition of mitochondrial alpha-ketoglutarate dehydrogenase by 1-methyl-4-phenylpyridinium ion. *Biochem Biophys Res Commun,* 143, 971-976.

Mori, H., Kondo, T., Yokochi, M., Matsumine, H., Nakagawa-Hattori, Y., Miyake, T., Suda, K. and Mizuno, Y. (1998) Pathologic and biochemical studies of juvenile parkinsonism linked to chromosome 6q. *Neurology,* 51, 890-892.

Narendra, D. P., Jin, S. M., Tanaka, A., Suen, D. F., Gautier, C. A., Shen, J., Cookson, M. R. and Youle, R. J. (2010) PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol,* 8, e1000298.

Narhi, L., Wood, S. J., Steavenson, S. et al. (1999) Both familial Parkinson's disease mutations accelerate alpha-synuclein aggregation. *J Biol Chem,* 274, 9843-9846.

Nieto, M., Gil-Bea, F. J., Dalfo, E. et al. (2006) Increased sensitivity to MPTP in human alpha-synuclein A30P transgenic mice. *Neurobiol Aging,* 27, 848-856.

Nishioka, K., Hayashi, S., Farrer, M. J. et al. (2006) Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. *Ann Neurol,* 59, 298-309.

Ozelius, L. J., Senthil, G., Saunders-Pullman, R. et al. (2006) LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med,* 354, 424-425.

Paisan-Ruiz, C., Jain, S., Evans, E. W. et al. (2004) Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron,* 44, 595-600.

Park, J., Lee, S. B., Lee, S. et al. (2006) Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. *Nature,* 441, 1157-1161.

Perez, R. G., Waymire, J. C., Lin, E., Liu, J. J., Guo, F. and Zigmond, M. J. (2002) A role for alpha-synuclein in the regulation of dopamine biosynthesis. *J Neurosci,* 22, 3090-3099.

Polymeropoulos, M. H., Lavedan, C., Leroy, E. et al. (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science,* 276, 2045-2047.

Pramstaller, P. P., Schlossmacher, M. G., Jacques, T. S. et al. (2005) Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. *Ann Neurol,* 58, 411-422.

Przedborski, S. and Vila, M. (2003) The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model: a tool to explore the pathogenesis of Parkinson's disease. *Ann N Y Acad Sci,* 991, 189-198.

Rideout, H. J., Larsen, K. E., Sulzer, D. and Stefanis, L. (2001) Proteasomal inhibition leads to formation of ubiquitin/alpha-synuclein-immunoreactive inclusions in PC12 cells. *J Neurochem,* 78, 899-908.

Satake, W., Nakabayashi, Y., Mizuta, I. et al. (2009) Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat Genet,* 41, 1303-1307.

Schapira, A. H., Cooper, J. M., Dexter, D., Jenner, P., Clark, J. B. and Marsden, C. D. (1989) Mitochondrial complex I deficiency in Parkinson's disease. *Lancet,* 1, 1269.

Shiba, K., Arai, T., Sato, S., Kubo, S. I., Ohba, Y., Mizuno, Y. and Hattori, N. (2009) Parkin stabilizes PINK1 through direct interaction. *Biochem Biophys Res Commun*.

Shimura, H., Hattori, N., Kubo, S. et al. (2000) Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. *Nat Genet,* 25, 302-305.

Simon-Sanchez, J., Schulte, C., Bras, J. M. et al. (2009) Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet,* 41, 1308-1312.

Smith, W. W., Pei, Z., Jiang, H., Dawson, V. L., Dawson, T. M. and Ross, C. A. (2006) Kinase activity of mutant LRRK2 mediates neuronal toxicity. *Nat Neurosci,* 9, 1231-1233.

Smith, W. W., Pei, Z., Jiang, H., Moore, D. J., Liang, Y., West, A. B., Dawson, V. L., Dawson, T. M. and Ross, C. A. (2005) Leucine-rich repeat kinase 2 (LRRK2) interacts with parkin, and mutant LRRK2 induces neuronal degeneration. *Proc Natl Acad Sci U S A,* 102, 18676-18681.

Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R. and Goedert, M. (1997) Alpha-synuclein in Lewy bodies. *Nature,* 388, 839-840.

Spira, P. J., Sharpe, D. M., Halliday, G., Cavanagh, J. and Nicholson, G. A. (2001) Clinical and pathological features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. *Ann Neurol,* 49, 313-319.

Valente, E. M., Abou-Sleiman, P. M., Caputo, V. et al. (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science,* 304, 1158-1160.

Vila, M., Vukosavic, S., Jackson-Lewis, V., Neystat, M., Jakowec, M. and Przedborski, S. (2000) Alpha-synuclein up-regulation in substantia nigra dopaminergic neurons following administration of the parkinsonian toxin MPTP. *J Neurochem,* 74, 721-729.

Vingerhoets, F. J., Snow, B. J., Tetrud, J. W., Langston, J. W., Schulzer, M. and Calne, D. B. (1994) Positron emission tomographic evidence for progression of human MPTP-induced dopaminergic lesions. *Ann Neurol,* 36, 765-770.

Vives-Bauza, C., Zhou, C., Huang, Y. et al. (2010) PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. *Proc Natl Acad Sci U S A,* 107, 378-383.

West, A. B., Moore, D. J., Biskup, S., Bugayenko, A., Smith, W. W., Ross, C. A., Dawson, V. L. and Dawson, T. M. (2005) Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. *Proc Natl Acad Sci U S A,* 102, 16842-16847.

West, A. B., Moore, D. J., Choi, C. et al. (2007) Parkinson's disease-associated mutations in LRRK2 link enhanced GTP-binding and kinase activities to neuronal toxicity. *Hum Mol Genet,* 16, 223-232.

Yamamura, Y., Sobue, I., Ando, K., Iida, M. and Yanagi, T. (1973) Paralysis agitans of early onset with marked diurnal fluctuation of symptoms. *Neurology,* 23, 239-244.

Yu, W. H., Matsuoka, Y., Sziraki, I., Hashim, A., Lafrancois, J., Sershen, H. and Duff, K. E. (2008) Increased dopaminergic neuron sensitivity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in transgenic mice expressing mutant A53T alpha-synuclein. *Neurochem Res,* 33, 902-911.

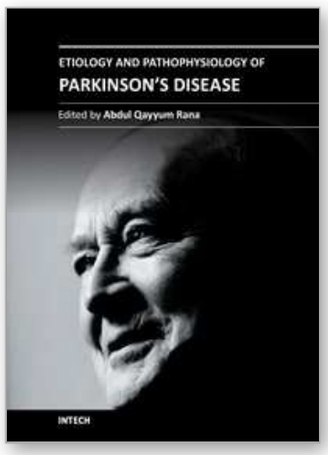
Zarranz, J. J., Alegre, J., Gomez-Esteban, J. C. et al. (2004) The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol,* 55, 164-173.

Zhang, N. Y., Tang, Z. and Liu, C. W. (2008) alpha-Synuclein protofibrils inhibit 26 S proteasome-mediated protein degradation: understanding the cytotoxicity of protein protofibrils in neurodegenerative disease pathogenesis. *J Biol Chem,* 283, 20288-20298.

Zimprich, A., Biskup, S., Leitner, P. et al. (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron,* 44, 601-607.

IntechOpen

IntechOpen



Etiology and Pathophysiology of Parkinson's Disease
Edited by Prof. Abdul Qayyum Rana

ISBN 978-953-307-462-7
Hard cover, 542 pages
Publisher InTech
Published online 12, October, 2011
Published in print edition October, 2011

This book about Parkinsonâ€™s disease provides a detailed account of etiology and pathophysiology of Parkinsonâ€™s disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinsonâ€™s disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinsonâ€™s disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinsonâ€™s disease.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Taku Hatano and Nobutaka Hattori (2011). Etiology and Pathogenesis of Parkinson’s Disease, Etiology and Pathophysiology of Parkinson's Disease, Prof. Abdul Qayyum Rana (Ed.), ISBN: 978-953-307-462-7, InTech, Available from: http://www.intechopen.com/books/etiology-and-pathophysiology-of-parkinson-s-disease/etiology-and-pathogenesis-of-parkinson-s-disease

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen