metabolism, immunity, and neurodegeneration (Tanaka et al., 2004). The ubiquitin system consists of three enzymes, i.e., the ubiquitin activating enzyme (E1), the ubiquitin conjugating enzyme (E2), and the ubiquitin-protein ligase (E3). The E3 transfers ubiquitin molecules to target proteins forming a polyubiquitin chain which is recognized by 26S proteasome as the proteolytic signal. Therefore, in the presence of mutated parkin proteins, accumulation of parkin-substrate proteins is expected to be the major cause of nigral neuronal death. However, to date there is no clear immunohistochemical evidence to indicate accumulation of parkin-substrates in PARK2 patients, despite many parkin-interacting proteins have been reported such as CDCrel-1 (Zhang et al., 2000), glycosylated alpha-synuclein (Shimura et al., 2001), PAEL receptor (Imai et al., 2001), and synphilin-1 (Chung et al., 2001). We recently reported that parkin-knock down SH-SY5Y cells showed increased formation of dopamine/dopa-derived quinones and apoptotic cell death (Machida et al., 2005); these quinones appeared to be the mediator of cell death. Thus parkin appears to have a potent anti-oxidative property. As in the case of sporadic PD, oxidative damage may be an important mechanism of nigral neuronal death in PARK2.

Other mechanism that has been postulated is polyubiquitylation at the lysine-63 residue of the ubiquitin molecules. Polyubiquitin chains formed via the lysine-48 residue of the ubiquitin molecule mainly become a marker for proteolytic attack by the 26S proteasome. On the other hand, lysine 63-linked polyubiquitylation has many biological roles other than proteolysis, such as endocytosis, DNA repair, translation, IkB activation, DNA silencing, virus budding, protein sorting, and protein trafficking (Tanaka et al., 2004). Parkin promotes not only polyubiquitylation at lysine-48 but also at lysine-63. Recently, Lim et al. (2005) reported that parkin enhanced lysine-63 mediated polyubiquitylation of synphilin-1. Thus this is a novel aspect of the functions of parkin protein, however, exact molecular mechanism of nigral neurodegeneration in PARK2 is still open to question.

PARK3

PARK3 is an autosomal dominant familial PD linked to the short arm of chromosome 2 at 2p13 (Gasser et al., 1998). The disease gene has not been identified yet. Clinical features are essentially similar to those of sporadic late onset PD; the age of onset was 36 to 89. Interestingly, penetrance was 40% suggesting that some apparently sporadic PD patients may represent PARK3. Dementia developed in two out of six original families (Gasser et al., 1998). Autopsy findings from those families showed nigral neurodegeneration and neurofibirillary tangles in cortical neurons.

Recently, Strauss et al. (2005) reported a missense mutation (G399S) in *HtrA2/Omi*, which has been mapped to the same locus (2p13), in 4 sporadic PD patients; cells overexpressing S399 mutation was reported to be more susceptible to stress-induced cell death than wild type. But this mutation was negative in the original families of PARK3.

HtrA2 is a serine protease that has extensive homology to bacterial heat shock endoprotease (Faccio et al., 2000). Interestingly this is a mitochondrial protein localized in the intermembrane space and is released from mitochondria upon apoptotic stimuli initiating apoptosis cascade by activating caspase 3 (Suzuki et al., 2001). This is a proapoptotic protein; nonetheless, its mutation in its PDZ domain (carboxy-terminal side) was associated with familial PD. Further interestingly, a mutation in the protease domain caused motor neuron degeneration type 2 in mice (Jones et al., 2003). Knockout mice were reported to have shown striatal neuronal loss (Martins et al., 2004). This gene appears to be an interesting addition to the research on familial PD.

PARK4

PARK4 is an autosomal dominant familial PD caused by triplication of *alpha-synuclein* (Singleton et al., 2003). This mutation was found in the large kindred, which has been designated as Spellman–Muenter–Waters–Miller family or Iowanian family. Initial family was reported by Spellman (1962) who reported an autosomal dominant family with PD in the United States. Then Muenter et al. (1998) made extensive clinical studies on this family. Another autosomal dominant family later reported by Waters and Miller (1994) was found to be another branch of the kindred reported by Spellman and Muenter. Clinical features consist of L-dopa responsive parkinsonism and dementia, which are consistent with clinical diagnosis of diffuse Lewy body disease. In autopsied patients, many cortical Lewy bodies were found in addition to nigral neurodegeneration with Lewy body formation.

This family was reported to be linked to the short arm of chromosome 4 (Farrer et al., 1999) but in fact the causative gene of this family was found to be triplication of *alpha-synuclein* (Singleton et al., 2003); the 1.5 Mb region including introns on both sides of *alpha-synuclein* was triplicated in a tandem fashion. Therefore, PARK4 should be reclassified as a form of PARK1.

PARK5

PARK5 is an autosomal dominant familial PD linked to the short arm of chromosome 4 at 4p14-p15.1. To date only one family is reported (Leroy et al., 1998). Clinical features are essentially similar to those of late onset sporadic PD; the age of onset was 49 to 50.

Leroy et al. (1998) found I93M missense mutation in the ubiquitin carboxyterminal hydrolase-L1 gene (*UCH-L1*) (Fig. 4). UCH-L1 is a neuron specific enzyme that cleaves carboxyterminal peptide bond of polyubiquitin chains; UCH-L1 is an ubiquitin recycling enzyme. I93M-mutated UCH-L1 has half of the catalytic activity of the wild enzyme (Leroy et al., 1998). The supply of ubiquitin for proteins that have to be destroyed by 26S proteasome may be reduced with this mutation. Interestingly homozygous deletion of exon 7 and 8 in mouse UCH-L1 causes gracile axonal dystrophy (*gad*) mouse; this is an autosomal recessive condition characterized by axonal degeneration and formation of spheroid bodies in motor and sensory nerve terminals (Saigho et al., 1999).

PARK6

PARK6 is an autosomal recessive young onset familial PD caused by mutations of *PINK1* (*PTEN-induced kinase 1*) (Valente et al. (2001). Clinical features of PARK6 are essentially similar to those of PARK2; the age of onset of the original family studied by Valente et al. (2001) ranged from 32 to 48, somewhat older than those of PARK2. Reflecting this later age of onset, dystonia and sleep benefit which are common to young onset PARK2 are usually not seen in PARK6 unless the age of onset is young.

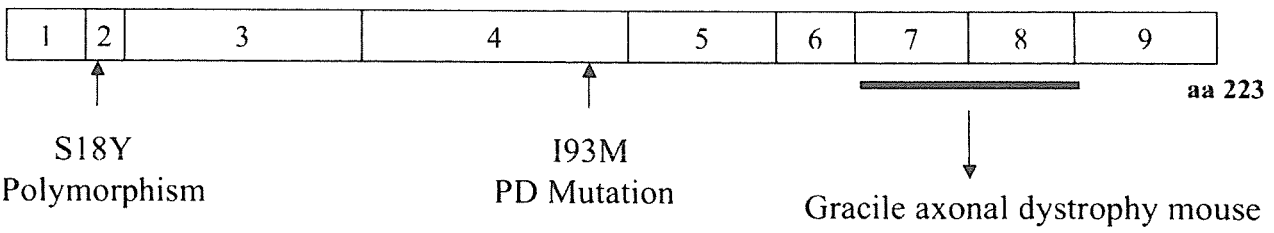

Fig. 4. Schematic presentation of exons of *UCH-L1* and its mutations. Only one mutation is known. I93M is associated with autosomal dominant PD. Interestingly homozygous exonic deletion involving exon 7 and 8 induces gracile axonal dystrophy (gad) mouse. S18Y polymorphism is said to confer neuroprotection for sporadic PD, but controversies exist

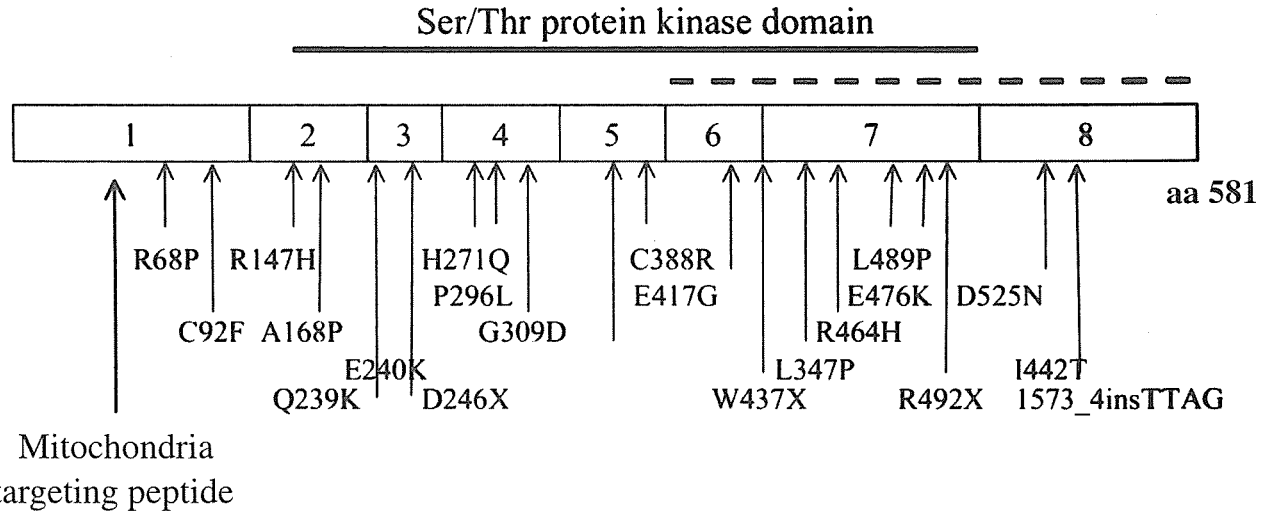

Fig. 5. Schematic presentation of exons of *PINK1* and its mutations summarized from the following literature, i.e., Valente et al. (2004), Hatano et al. (2004), Heary et al. (2004), Rohe et al. (2004), and Li et al. (2005). As PINK1 is a mitochondrial protein, it has a mitochondria-targeting sequence (exon 1). Two mutations in this targeting sequence are also known. Many missense and nonsense mutations are reported. Recently, we found an exonic deletion involving exon 6 to 8 indicated by the broken line. The solid line indicates the catalytic domain

PINK1 has been mapped to the short arm of chromosome 1 at 1p35-p36 (Valente et al., 2004). To date, 17 missense mutations, 3 nonsense mutations, one insertion, and one exon deletion are known (Valente et al., 2004; Hatano et al., 2004; Heary et al., 2004; Rohe et al., 2004; Li et al., 2005) (Fig. 5). We recently found a novel missense mutation (C388R) and an exonic deletion from exon 6 to 8; the latter was the first documented case with exonic deletion mutation in PARK6 (Li et al., 2005). PARK6 appears to be the second most common autosomal recessive PD after PARK2.

PINK1 is a mitochondrial matrix protein and has a protein kinase activity, however, its exact functions are not known. PINK1 stands for PTEN-induced kinase 1. PTEN stands for protein tyrosine phosphatase with homology to tensin: *PTEN* is a tumor suppressor gene on chromosome 10 mutated in many human tumors (Steck et al., 1997).

PARK7

PARK7 is an autosomal recessive familial PD caused by mutations of *DJ-1* (Bonifati et al., 2003). Clinical features are essentially similar to those of PARK2 including the age of onset, which is younger than that of PARK6. Affected patients show L-dopa-responsive parkinsonism of varying severity and drug-induced motor fluctuation and dyskinesia. Interestingly, three out of four patients in the original family showed psychiatric disturbances (anxiety attacks) (Dekker et al., 2003). Atypical clinical features include short statue and brachydactyly, which were found in Dutch kindred (Dekker et al., 2004).

DJ-1 has been mapped to the short arm of chromosome 1 at 1p36 and was identified as a novel oncogene that transformed mouse NIH3T3 cells in cooperation with activated Ras (Nagakubo et al., 1997). To date, 6 missense mutations, 1 intronic mutation, 1 small deletion, and 2 exonic deletions (exon 1 to 5 and exon 5 to 7) are known (Bonifati et al., 2003; Abou-Sleiman et al., 2003; Hague et al., 2003; Hering et al., 2004) (Fig. 6). *DJ-1* mutations are rare compared with *parkin* and *PINK1* mutations. We could not find *DJ-1* mutations among Japanese PD families studied.

DJ-1 is a potent anti-oxidative protein and this character depends on its 106-cysteine residue (Taira et al., 2004). DJ-1 is a cytoplas-

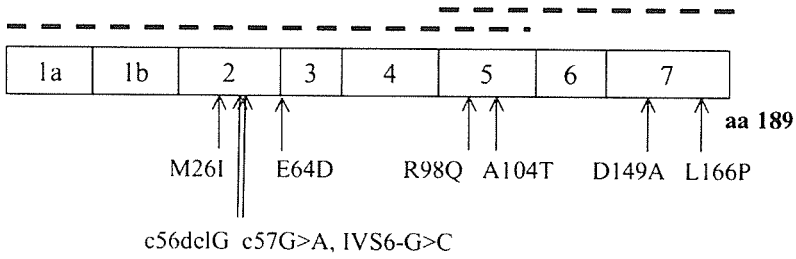

Fig. 6. Schematic presentation of exons of *DJ-1* and its mutations summarized from the literature, i.e., Bonifati et al. (2003), Abou-Sleiman et al. (2003), Hague et al. (2003), and Hering et al. (2004). Exon 1 and 2 are spliced out in the mature protein. Broken lines indicate exonic deletions

mic protein (Bonifati et al., 2003); however, oxidized DJ-1 is relocated to mitochondria (Canet-Aviles et al., 2004). DJ-1 undergoes dimmer formation to become active (Honbou et al., 2003; Tao and Tong, 2003). One of the PD-inducing missense mutations, L166P, interferes with dimmer formation (Wilson et al., 2003) and is degraded more rapidly than wild DJ-1 by ubiquitin-proteasome-system (Macedo et al., 2003; Miller et al., 2003) or by autoproteolysis (Gorner et al., 2004). This mutant DJ-1 is also mislocalized to mitochondria. Further interestingly, parkin interacts with mutated DJ-1 (L166P) but not with wild one (Moore et al., 2005), suggesting that parkin might be acting as a quality control protein for DJ-1. Thus molecular mechanism of nigral neuronal death in PARK7 appears to be at least in part related to dysfunction of anti-oxidative property of DJ-1.

PARK8

PARK8 is an autosomal dominant PD caused by mutations of *LRRK2/dardarin*. Clinical features were first described in large Japanese kindred (Nukada et al., 1978). They reported 36 patients in 5 generations. The age of onset ranged from 38 to 68 (mean = 53). Later the mean age of onset was reported as 51 ± 6 as the number of affected members increased (Funayama et al., 2002). Initial symptom was either gait disturbance or rest tremor. All of them showed L-dopa-responsive parkinsonism. Motor fluctuations and psychiatric side effects from L-dopa treatment can be seen. Clinical features are essentially similar to those of late onset sporadic PD except for slightly younger age of onset. Post-mortem examination in four patients from the original family showed pure nigral degeneration without Lewy body formation (Funayama et al., 2002). But later on another patient who came to autopsy from the same family showed nigral degeneration with Lewy bodies (Personal communication with Dr. K. Hasegawa).

The Western Nebraska family (Family D) reported by Wszolek et al. (1995), which inluded 18 patients in 5 generations, turned out to be PARK8. The age of onset was 48 to 78 (mean 63). Neuropathological features of this family are very interesting in that among the four patients who came to autopsy, one patient showed brain stem type Lewy body pathology; the second patient showed diffuse Lewy body disease pathology; the third patient showed nigral neuronal loss and gliosis with neurofibrillary tangles in the remaining nigral neurons without Lewy body formation; the fourth patient showed marked neuronal loss and gliosis in the nigra and locus coeruleus without any inclusions or tau-positive accumulations (Wszolek et al., 2004). Four different pathological findings in the same family would indicate the difficulty of defining a disease entity by neuronal inclusions. Family A reported by Denson and Wszolek (1995) was also turned out to be PARK8.

PARK8 has been mapped to the centromeric region of chromosome 12 (Funayama

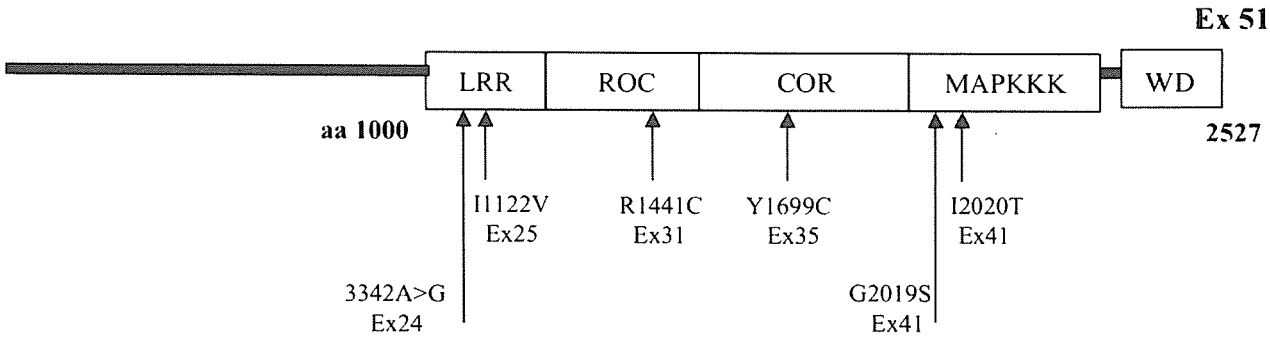

Fig. 7. Schematic presentation of *LRRK2* and its mutations summarized from the literature, i.e., Zimprich et al. (2004), Paisan-Ruiz et al. (2004), and Kachergus et al. (2005). LRRK2 protein belongs to ROCO protein family, which is characterized by the presence of ROC domain and COR domain. Many of the ROCO proteins also have LRR, MAPKKK, and WD domains. See the text for the explanations of these domains. To date 6 missense mutations have been reported in the homology region. Exon 41 appears to be a mutational hot spot

et al., 2002). The causative gene was identified as *LRRK2/dardarin* (Zimprich et al., 2004; Paisan-Ruiz et al., 2004). LRRK2 stands for leucine-rich repeat kinase 2 and dardar means tremor in the Bask language where families of PARK8 are found. *LRRK2* is a huge gene encompassing 144 kb and the open reading frame consists of 1449 base pairs in 51 exons. LRRK2 protein consists of 2527 amino acids and it is ubiquitously expressed in the cytoplasm of many organs. To date 6 missense mutations have been reported (Zimpricht et al., 2004; Paisan-Ruiz et al., 2004; Nichols et al., 2005) (Fig. 7).

LRRK2 protein belongs to the ROCO protein family. ROCO proteins are a group of proteins which has ROC and COR domain (Bosgraaf and Haastert, 2003). ROC stands for Ras in complex proteins belonging to the Ras/GTPase superfamily, and COR stands for carboxy terminal of ROC. In addition, many ROCO proteins have a LRR (leucine-rich repeat) domain, which has 3 to 16 leucine-rich repeats, a MAPKKK (mitogen-induced protein kinase kinase kinase) domain, and a WD domain, which is rich in tryptophan and aspartate repeats. The function of LRRK2 is still unknown but as it has protein kinase domain, it is likely that its role is phosphorylation of proteins that are important for the survival of nigral neurons. It is interesting to note that alpha-synuclein aggregates in PD are highly phosphorylated in Ser-129 (Fujiwara et al., 2002); therefore, it is an interesting question whether or not LRRK2 is in some way related to phosphorylation of alpha-synuclein.

PARK9

PARK9 is an autosomal recessive familial PD linked to the short arm of chromosome 1 at 1p36 (Hampshire et al., 2001). The causative gene has not been identified. Clinical features consist of L-dopa-responsive parkinsonism, supranuclear gaze palsy, pyramidal sign, and dementia, called Kufor-Rakeb syndrome. The age of onset is 10 to 20. Neuropathologically not only the substantia nigra but also the pyramidal tract, putamen, and the pallidum show neurodegeneration. PARK9 appears to be a form of multiple system atrophy.

PARK10

The PARK10 is linked to the short arm of chromosome 1 at 1p32. This locus was found by genome wide scanning on familial as well as sporadic cases of PD in Iceland (Hicks et al., 2002); they studied 117 PD patients and 168 of their unaffected relatives within 51 families using 781 microsatellite markers. The mean age of onset was 65.8. They showed linkage to chromosome 1p32 with a lod score of 4.9. The disease gene has not been identi-

fied yet. As expected from the source of the clinical subjects, clinical features are essentially similar to those of sporadic PD.

PARK11

PARK11 is an autosomal dominant familial PD linked to the long arm of chromosome 2 at 2q36 to q37 (Pankratz et al., 2003). The causative gene has not been identified yet. Clinical features are essentially similar to those of sporadic PD with the mean age of onset at 58. Neuropathological findings are not known.

Other forms of familial PD

There are many families in which linkage analysis failed to show linkage to any one of the known loci that are associated with familial forms of PD. Such reports are increasing every year. According to our hands, we have analyzed 347 families for known PD-causing genes including non-Japanese families with either autosomal dominant or recessive inheritance. We found 116 families with *parkin* mutations, 8 families with *PINK1* mutations, no *DJ-1* mutation, 10 families with *LRRK2* mutations, and 2 families with *alpha-synuclein* duplication. Overall mutation rate was 136 positive families out of 347 (39.2%). In another word, approximately 60% of familial patients with PD did not have known mutations. Mutual relationship among the familial PD causing proteins is an interesting and important subject to study. Identifying new genes for familial PD would give us important information on this topic. Such information would also give us important clues to investigate pathogenesis of sporadic PD.

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第2章　病因・病理と病態生理

病因・発症機序

要旨

高齢化社会に向けてパーキンソン病の罹患率は今後さらに増えることが予想される．ドパミンの補充療法以来，生命予後は劇的に改善しているものの，一生涯薬物療法から解放されることのない生活を強いられている．さらに，長期服用に伴う合併症の問題もクローズアップされており，満足のいく治療とは言い難いのが現状である．進行阻止ができれば生活レベルも高いままで維持できることから，本質的な原因究明が望まれている．遺伝性パーキンソン病の研究が大きな手掛かりとなるものと考える．

●キーワード

家族性パーキンソン病
ミトコンドリア機能低下
酸化ストレス
ドパミン代謝
タンパク分解系

はじめに

パーキンソン病（PD）の多くは家族内発症のない孤発型であるが，一部に家族内発症の認める家族性 PD（FPD）が存在する．最初に同定報告された α－シヌクレインの点変異は極めてまれな原因遺伝子あるが，FPD の有無にかかわらず病理診断で不可欠な細胞質内封入体であるレヴィー小体の主要構成タンパクであることが分かっている．このように単一遺伝子の機能が孤発型 PD（SPD）の病態に直接的にかかわっていることが徐々に判明しており，今後，FPD からのアプローチが SPD の病態解明に最も有効な戦略になりうると考えている．また，*PARK8* の浸透率は 80 歳で 100％ に達することより，全発症年齢に FPD も分布することが分かっている．このことは SPD においても遺伝的素因の関与が高いことが推定される．事実，最近の報告では 66 歳を若年性 PD として，それより若い PD 患者においては家族内発症の相対危険度は 2 倍を超えるとされている．

このようにますます FPD の研究は重要になってきており，FPD のアプローチから黒質神経変性の機序を明らかにできると考えている．本稿では，黒質神経変性の発症機序について，FPD の最近の進

表1 家族性パーキンソン病（FPD）の分類

FPD	遺伝形式	遺伝子座	遺伝子	LB
PARK1, 4	常優	4q21−q23	*α−syn*	＋
PARK2	常劣	6q25.2−27	*parkin*	−*
PARK3	常優	2p13	?	＋
PARK5	常優	4p14	*UCH−L1*	＋
PARK6	常劣	1p35−p36	*PINK1*	?
PARK7	常劣	1p36	*DJ−1*	?
PARK8	常優	12p11q13.1	*LRRK2*	＋/−
PARK9	常劣	1p36	?	?
PARK10	感受性	1p32	?	?
PARK11	常優	2q36−37	?	?

*：一般にレヴィー小体は観察されないが，変異によっては観察されることがある．
剖検脳については，ヘテロ接合体でレヴィー小体の報告はあるが，ホモ接合体での有無について報告がない場合は？とした．
常優：常染色体優性，常劣：常染色体劣性，LB：レヴィー小体（Lewy body）

歩から我々のデータを踏まえて解説したい．

家族性パーキンソン病の分類と臨床型

現在のところ PARK11 までの報告があり，そのうち6つの原因遺伝子が同定されている．常染色体優性遺伝性パーキンソン病（ADPD）では，*SNCA*（点変異および正常型 SNCA の重複），*UCHL−1*，*Nurr1* が，常染色体劣性遺伝性パーキンソン病（ARPD）では，*parkin*，*DJ−1*，*PINK1* が同定された（表1）．PARK10 は PD の疾患感受性遺伝子としてマップされている．一般に ARPD は若年発症することが多く，一方 ADPD は中高年で発症することが多い．もちろん例外もあり，今後遺伝子のタイプが同定されてくるといろんな情報が分かってくると思われる．上記の遺伝子のうち，日本人では ARPD では，*parkin*，*PINK1* 変異が，ADPD については，PARK8 の原因遺伝子 *LRRK2* 変異が存在する．さらに，PARK4 と分類され SNCA の重複型が存在することが報告された．

日本は島国であり近親婚が多かったという地理的歴史的背景もあり，ARPD が圧倒的に多いとされていたが，ADPD も少なからず存在することが分かっており，FPD も多岐にわたって存在することか

ら，今後新規遺伝子の報告がされていくものと思われる．

常染色体優性遺伝性パーキンソン病（ADPD）

1．α－*synuclein*（PARK1，4）

1997 年から 1998 年にかけてヨーロッパの ADPD の家系においてα－シヌクレイン（SNCA）が原因遺伝子であることが最初に報告された[1]．最初に A53T が，次に A30P の 2 つの点変異が報告された．A53T は共通の祖先から生じる創始者効果が示唆されている．その後スペインの家系において新たな点変異 E46K が認められ，さらに PARK4 としてマップされていた Iowa 家系にて 3 倍体（triplication）による変異が報告された[2]．剖検脳において mRNA レベルでの過剰発現が示され，遺伝子発現レベルの増加がその病態にかかわっていることが推定されている[1]．事実，SNCA の過剰発現系の齧歯類モデルやショウジョウバエモデルにおいて，このタンパクの過剰発現がタンパクの異常凝集やドパミン神経細胞への毒性を示すことが報告されている．Multiplication については追試により 3 倍体がさらに 1 家系，2 倍体（duplication）の症例が 3 家系存在することが分かった．3 倍体ではびまん性レヴィー小体病を，2 倍体では認知症を伴わない PD を呈するとされ *SNCA* のコピー数の違いが痴呆の有無を惹起されるものと推定された．その後，我が国でも 2 倍体の報告が少なくとも 2 家系存在することが分かった[3]．我が国で見いだされた 2 倍体は痴呆症状が存在していたが，パーキンソニズム発症後数年後に痴呆症状が発現しており，コピー数に依存して臨床型の重度が規定されている可能性が考えられた．また，同じ SNCA の 2 倍体でも，2 倍体の範囲の違いが臨床症状に影響を与えている可能性も考えられ，我が国で認められた 2 倍体の家系は 2 倍体の範囲が既報症例より広いことが分かっており，その違いが痴呆症状の発現に影響を与えている可能性が考えられた．

SNCA の機能については依然不明であるが，局在が脂質ラフトにあり，シナプス小胞のダイナミクスにかかわっており，学習や神経の可塑性に関与していることが推定されている．また，SNCA はチロシン水酸化酵素を抑制しながらドパミン産生を制御していることも報告されている．さらに，SNCA はホスホリパーゼ D_2（PLD_2）を抑制

することが報告されている[4]．PLD_2 は，脂質を介在したシグナルカスケードや膜輸送に関与することが分かっており，SNCA の膜輸送やシナプス小胞輸送への関与が推定される．興味深いことにドパミン神経様特徴を持つ細胞に対しては過剰発現が毒性を示すのに対し，非ドパミン神経に対しては神経保護的に作用することが報告されている．このことは，ドパミン神経細胞ではむしろ過剰発現とともに活性酸素種の産生が増加することが想定されている．

SNCA と酸化ストレスの関与に加えてミトコンドリア機能への関与も報告されている．SNCA 過剰発現のマウスでは，ミトコンドリア機能の変化が観察され，その結果細胞死が惹起される．また，SNCA ノックアウトマウスでも，ミトコンドリア内の脂質異常と電子伝達系の機能低下が報告されており，SNCA もまたミトコンドリア機能への関与が指摘されている．

2．*LRRK2*（PARK8）

相模原地方の大家系から遺伝子座が決定され，*LRRK2* がその原因遺伝子であることが判明した[5]．最初に LRRK2 変異が同定された家系はスペインの Basque 地方の家系で，振戦が目立つことから原因遺伝子を振戦を意味する“dardarin”と命名された．その後，この遺伝子はすでに報告されていることもあり，LRRK2 が一般的に用いられている．この遺伝子変異はエクソンが 51 個もあり，多岐に変異が分布している．

最も頻度の高い変異は G2019S 変異で白人の FPD の 5％，SPD の 1～5％ を示すホットスポットとなっている．我が国でも陽性率は優性遺伝性の 5.8％ で，SPD を含めて 1.7％ に認めた[6]．この G2019S 変異は創始者効果が認められると報告されているが，我が国の症例ではハプロタイプを共有していないことより創始者効果は白人に限っている可能性がある．しかしながら，人類の民族移動とともに変異が動いている可能性があり，アメリカ大陸でこの変異頻度が低いことから狭い範囲でハプロタイプを共有する可能性も残っている．

LRRK2 の局在に関しては，変性した神経線維に局在しているもののレヴィー小体には存在していない．詳細な機能については不明だが，キナーゼドメインを持つことよりそのリン酸化の関与が指摘されている．変異 G2019S，I2020T ではキナーゼ活性が増加することが指摘

されている．この gain－of－function 効果により PD の発症することが推定されている．また，興味深いことに LRRK2mRNA の発現パターンは黒質では発現せず，ドパミン投射先である線条体，皮質，小脳で，その発現が観察されている．mRNA は核で産生されるので，積極的に投射先に輸送されていることが予想される．

LRRK2 変異においては，レヴィー小体の有無は同じ変異の家系でもその存在は一定していない．また，同じ家系でも神経病理学的には，SNCA やタウタンパクがさまざまな程度で蓄積している．臨床的には，典型的な PD から進行性核上性麻痺様，多型統萎縮症，運動ニューロン病まで多彩な症状を呈している．この LRRK2 が重要な意味合いを持つのは，α－シヌクレインやタウタンパクの上流に位置する可能性が高いからである．

常染色体劣性遺伝性パーキンソン病（ARPD）

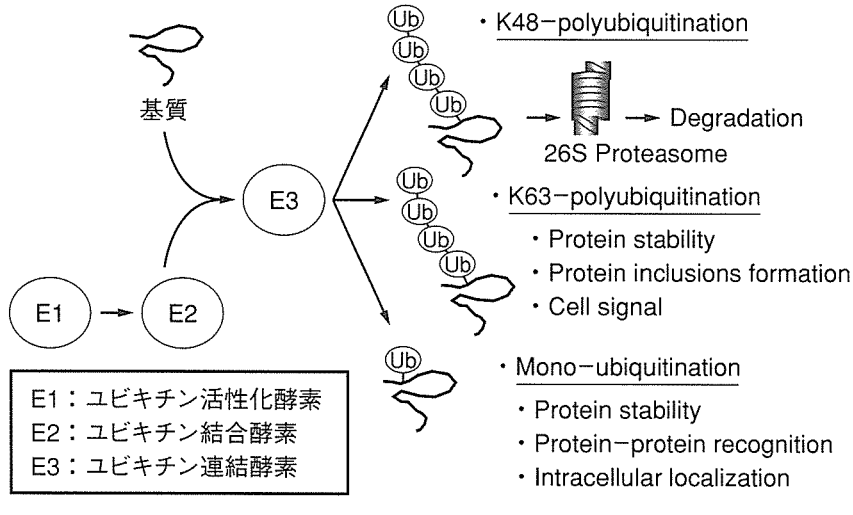
1．*parkin*（PARK2）

1973 年に Yamamura らによりその臨床型が確立され，我々のチームにより遺伝子単離が行われた[7]．機能についても，選択的タンパク分解系であるユビキチン・プロテアソーム系のユビキチンリガーゼであることを世界に先駆けて報告した．細胞死の機序としては，基質の蓄積の寄与が推定されている[9]．つまり，基質が parkin により分解されずに蓄積することで細胞死が誘導される機序が提唱された[8]．現在 14 種類の基質候補が報告されているが，共通しているのはいずれも膜関連タンパクである（表2）．しかしながら，最近になり parkin のリガーゼ機能については，① ユビキチン分子内の 48 番目リジンのポリユビキチン鎖付加（K48），② 63 番目のポリユビキチン鎖付加（K63），③ モノユビキチン付加（mono 化）の3パターンが存在する（図1）ことが報告された．K48 はタンパク分解系に関与し，K63 はタンパクの安定化，封入体形成，細胞シグナルに関与が指摘されている．一方，mono 化はタンパクの安定性，タンパクの認識，細胞内局在の関与が推定されている．Parkin に関してはいずれのユビキチン修飾にも関与していることが報告されている[9]．Parkin にはさまざまな機能を持っている可能性があり，その細胞内局在もミトコンドリアからゴルジまで多岐にわたっていることが報告されている．

表2 基質候補

基　質	機　能	報告者
CDCrel−1	Exocytosis	Zhang Y, et al.（2000）
CDCrel−2	Exocytosis	Choi P, et al.（2003）
Pael−receptor	ER stress	Imai Y, et al.（2001）
O−gly. a−synuclein	Lewy body	Shimura H, et al.（2001）
Synphilin−1	Lewy body	Chung KK, et al.（2001）
Cyclin E	Apoptosis	Staropoli J, et al.（2003）
a / b Tubulin	Microtubules	Ren Y, et al.（2003）
Synaptotabmin XI	Fusion or Docking	Huynh DP, et al.（2003）
p38 subunit of aminoacyl −tRNA synthase	Protein biosynthesis	Corti O, et al.（2003）
Poly−Q protein	Poly−Q disease	Tsai Y, et al.（2003）
Single−minded（SIM2）	Transcription factor	Okui M, et al.（2005）
Misfolded DAT	Dopamine transporter	Jiang H, et al.（2004）
RanBP2	E3 SUMO ligase	Won Um J, et al.（2006）

図1 ユビキチン修飾の分類



ユビキチン化には，48 番目のリジン残基にポリユビキチン鎖が付加される場合，63 番目のリジン残基にポリユビキチン鎖が付加される場合，モノユビキチン化される場合の 3 種類が存在する．K48 のポリユビキチン鎖は，26S プロテアソームに認識される分解シグナルとなる．詳細は文中を参照のこと．

機能に関しては，モノアミン酸化酵素の mRNA の抑制や活性の低下が，患者で見いだされた変異 parkin で観察されていることが報告されている．我々のグループでは，parkin がドパミンキノン体の産生抑制にかかわっていることを指摘している[10]．また，ドパミン分子による修飾により parkin の機能が不活化されることを報告している．酸化ストレスによる parkin の不活化が起れば，SPD の病態にも parkin の関与が十分に考えられる．また，このドパミンキノン体の産生は SNCA で抑制されることを見いだしている．Parkin のリガーゼ活性に関してはシャペロンに属する 14–3–3η により活性が制御されていることを報告している[11]．この 14–3–3η も SNCA と結合することより FPD の遺伝子産物が共通カスケードを形成していることが分かっている．

変異に関しては，ARPD の約半分がこの parkin 遺伝子変異によることが報告されており，最も頻度の高いタイプである．変異型としては，外国ではミスセンス変異および microdeletion が多い一方，我が国ではほとんどが欠失変異である．臨床症状としては，典型的なパーキンソニズムから Yamamura らにより報告された特徴的臨床症状のほかに，小脳症状など多彩な表現型の報告がある．遺伝子変異型と表現型との相関ははっきりしないが，C末端にある RING ドメインに変異があるとヘテロ接合体でも若年発症する可能性が指摘されている．

2．*PINK1*（PARK6）

シシリア島の ARPD の家系を対象とした連鎖解析により 1p35–36 に遺伝座が絞られ，*PINK1*（PTEN Induced Putative Kinase 1）遺伝子がその原因であることが報告された[12]．この PINK1 変異は世界中に分布しており，多くは点変異であるが，我が国でもその存在が確認されている[13]．興味深いことに早期発症の孤発型（50 歳以下）においても，ヘテロ接合体での変異も報告されている．*PINK1* 遺伝子は 581 のアミノ酸からなり，最初の 34 のアミノ酸残基にミトコンドリアへの移行シグナルを持ち，後半の大部分をカルモジュリンファミリーのセリン/トレオニンキナーゼドメインが占める．このドメインに変異が集中している．これまでにミトコンドリアへの局在および酸化ストレスにより引き起されるミトコンドリアの機能障害と，アポトーシスの誘導に対して保護的に働いていることが実験的に示されてい

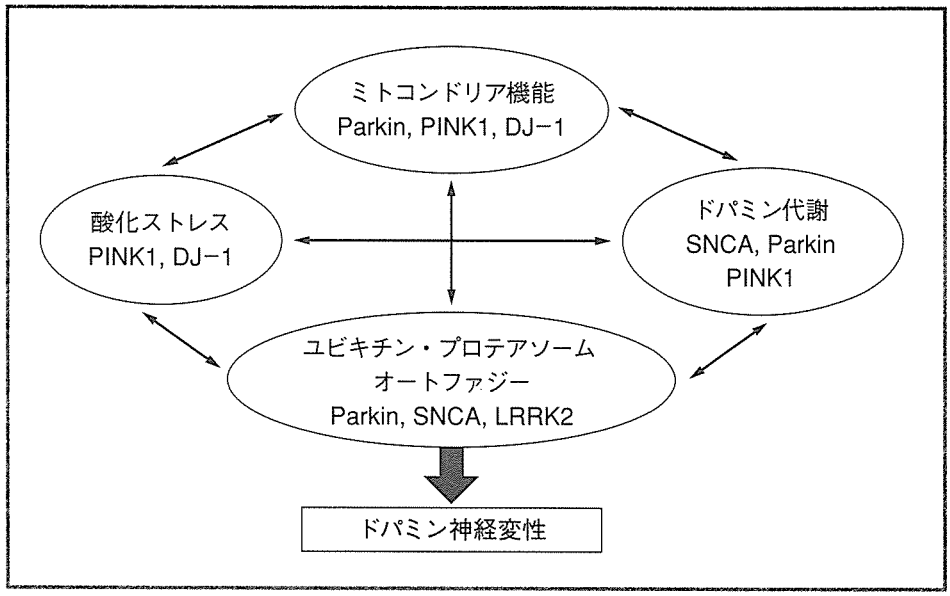
る．PINK1 はレヴィー小体にも存在していることが報告されており，*in vivo* での実験系で PINK1 が不溶性になりやすい性質と関連があるかも知れない．また，PINK1 局在は神経細胞とグリアにある．最近になり PINK1 ノックアウトショウジョウバエではミトコンドリアのクリステの膨大に伴うミトコンドリア機能低下が指摘されており，parkin ノックアウトショウジョウバエの極めて類似性の高い表現型を持つことが分かった．さらに，この PINK1 ノックアウトショウジョウバエに parkin を過剰発現させてやるとミトコンドリア機能は回復することが分かった．面白いことに parkin ノックアウトショウジョウバエに PINK1 を過剰発現させてもミトコンドリア機能を回復させることができなかった[14]．このことは PINK1 が parkin の上流に位置することを示すものである．

3．*DJ－1*（PARK7）

ヨーロッパの ARPD の家系を対象とした連鎖解析により 1p36 にマップされ，原因遺伝子として *DJ－1* 遺伝子が同定された[15]．オランダの家系において exon1 から 5 にまたがる欠失が見いだされ，イタリアの家系にて L166P の点変異が見いだされた．*DJ－1* は 189 のアミノ酸から構成され，脳も含め体内の各組織にユビキタスに発現している．結晶構造からは二量体を形成していることが分かっており，局在はミトコンドリアマトリックスや内膜に存在することが報告されている[16]．この局在からは PINK1 と相互作用の可能性を示すものである．

DJ－1 には SNCA を始めとするタンパクの凝集抑制作用があり，このシャペロン作用は残基 106 のシステインにより増強される[17]．もちろん，過度の酸化は機能低下になる．おそらく DJ－1 の主要な作用としては，シャペロン作用と抗酸化ストレス作用にかかわっていることが推定される[18]．変異頻度は大規模調査にても陰性例が多く，まれな変異である可能性が示唆されている．我が国でも DJ－1 変異は一例も存在しない．

図2　家族性パーキンソン病における共通機序そして孤発型パーキンソン病の解明へ



おわりに（図2）

SPD の病態には酸化ストレス，ミトコンドリア機能低下，ドパミン代謝異常などの関与が指摘されていた．しかしながら，詳細な解析となると MPTP－PD モデルを使った解析に限られており，なかなかブレイクスルーが生まれなかった．しかしながら，FPD の研究により詳細な機能解析が可能になり，しかも遺伝子産物は共通したカスケードを形成していることが分かってきている．重要なのは，これら遺伝子産物の機能は酸化ストレス，ミトコンドリア機能低下，ドパミン代謝，そしてタンパク分解系にかかわっており，SPD の病態と共通機序を形成していることは間違いないと考えている．今後，これら遺伝子産物の相互作用を明らかにできれば，黒質神経細胞変性の機序を明らかにできる日もそう遠くないと考える．

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