effects and how to manage drug-induced psychotic symptoms should they arise.[15]

Regarding attitudes towards drug intake and dose increases, it is noteworthy that while almost all US physicians believe patients would rather reduce their pill burden, US patients themselves consider their biggest challenge to be wearing-off. In contrast, patients in Japan would rather increase their dose or dosing frequency in order to ameliorate their symptoms. Indeed, patients in Japan expressed a preference for obtaining symptomatic relief, even if that required an increase in medication dosing. This observation is strengthened further by the fact that this preference for symptomatic relief was similar between patients with or without wearing-off. In addition, one major discrepancy between patients and physicians, in both the US and Japan, related to dose increases. In the US, patients feared wearing-off, yet physicians were under the impression that patients wanted to restrict medication intake; However, in Japan, patients seek symptomatic relief, even if that results in an increase in medication. Despite this, the conference survey results indicated that physicians in Japan are reluctant to increase doses. This is supported by results of Japanese studies advocating the use of low doses of levodopa to avoid the development of motor complications.[12] Therefore, the findings demonstrate a need for improved communication between doctors and patients in both countries regarding dose increases, taking into account patient perspectives of adverse effects.

The difference between patient perspectives among Japanese and US patients is likely to stem from differences in medical practice for the management of PD. However, the underlying reasons for this difference are unclear. One possibility is that availability of certain antiparkinsonian therapeutic agents in the two countries may differ. For example, the triple combination therapy levodopa/carbidopa/entacapone is not yet available in Japan, whereas certain dopamine agonists, such as talipexole and droxidopa, are only marketed in Japan. Monotherapy with selegiline is not covered by Japanese health insurance, because it has not been approved by the local authorities.[16] Another possible difference that may influence decisions on therapy is the cost of the drug in the respective countries. In Japan, the cost of antiparkinsonian therapies is largely covered by government-funded Japanese health insurance. In the US, the cost of the drugs depends on the specific health care insurance scheme in which the patient in enrolled. However, given that the cost of levodopa is much lower than that of dopamine agonists, it is unlikely to play a significant role in determining whether to introduce levodopa or whether increases in its dosage or dosing frequency are required.[17] In fact, in Japan, the cost of levodopa and dopamine agonists will be covered by national insurance (at least for patients with Hoehn and Yahr stage III or higher), and is unlikely to be a driving factor for the choice of therapy used in this region. Therefore, the reason why the doses of levodopa used in Japan tend to be lower than in the West is unclear. Results from a retrospective study based at the Sapporo Azabu Neurosurgical Hospital in Japan suggested that lower doses of levodopa may be sufficient to achieve symptom control and may reduce or delay the appearance of motor complications compared with the higher doses of levodopa required to achieve symptom control in multinational, randomized, controlled trials.[12,18–20] The authors of the former study proposed that Japanese patients with PD may respond better to levodopa compared with their Caucasian counterparts, and speculated that variations in genetic background, pharmacokinetics, and lifestyle choices may contribute to this difference.[12] It is also likely that physicians in Japan are concerned about dyskinesias, which tend to be associated with levodopa, and try as much as possible to avoid the development of this complication.[12] Finally, a long-term anti-levodopa campaign, which focused on the potential neurotoxicity of levodopa, and interpretation of the 2002 Japanese practice guidelines for PD, may play a role in influencing attitudes in Japan.[16,21] Although, the seminal ELLDOPA (Earlier vs Later L-DOPA) study of levodopa in early PD patients has dispelled the notion that levodopa is neurotoxic,[22] concerns may still resonate with many Japanese physicians. However, underdosing with levodopa can be associated with a reduction in symptom control and, consequently, may impact patient quality of life.[5] In addition, the observations that dyskinesia is not a major concern for patients in this study and that patients in Japan prefer increasing the dose of medication to improve symptom control, suggests that physicians should not limit the dose of levodopa to avoid the development of dyskinesia.

This study set out to elucidate the perspectives of patients towards PD and antiparkinsonian therapy and to understand whether such views and concerns differ between patients in the US and those in Japan. Although in some cases (eg, those with cognitive or physical difficulties), the patient's caregiver may have completed the Japanese survey on behalf of the patient, this is unlikely to have affected the study results significantly. However, it should be noted that the way in which the two surveys were conducted varied slightly, and the results between the two countries may not be directly comparable. As such, some caution must be exercised when interpreting these results. Nevertheless, the study highlights some interesting similarities and differences between the

two populations, as well as differences between patient and physician perspectives in both countries.

## Conclusion

In conclusion, this study suggests that patient perceptions about PD therapy may differ from the views of their physicians. Heightened understanding of patient concerns and attitudes towards PD treatments and their associated complications may help physicians to individualize optimal treatment strategies. Improving patient education and awareness about PD and medical therapy will be instrumental in enhancing patient–physician communication and, consequently, patient care and treatment outcomes.

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# Citation Classic

# Parkin and Parkinson Disease

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**Featured Article:** Shimura H, Hattori N, Kubo S, Mizuno Y, Asakawa S, Minoshima S, et al. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet 2000;25:302–5.[5]

Since the 1970s, Japanese neurologists have described patients with autosomal recessive forms of familial Parkinson disease (PD),[6] which have been termed "autosomal recessive juvenile parkinsonism" and "early-onset parkinsonism with diurnal fluctuation," both of which have become known as "PARK2" *(1)*. We attempted to identify the gene responsible for autosomal recessive familial PD. In 1997, we identified, along with our collaborators, an autosomal recessive familial PD gene between D6S437 and D6S264 *(2)*, and in 1998 we found that mutations in that gene were linked to autosomal recessive familial PD. We designated the gene, formerly known as *parkin*, as *PARK2*[7] [parkinson protein 2, E3 ubiquitin protein ligase (parkin)] *(3)*. Parkin is a 465-amino-acid protein containing an N-terminal ubiquitin-like domain linked to a C-terminal RING box. A year later, we demonstrated that parkin was produced in the substantia nigra and localized in Lewy bodies *(4)*. The function of parkin remained unknown, however. In 2000, in collaboration with Keiji Tanaka, Toshiaki Suzuki, Tomoaki Chiba, Shin-ichiro Kubo, Kazuhiro Iwai, Shuichi Asakawa, Shinsei Minoshima, and Nobuyoshi Shimizu, we were able to identify parkin as a ubiquitin-protein ligase that facilitates the degradation of proteins that interact with ubiquitin-conjugating enzyme UbcH7. We reported our results in the *Nature Genetics* article featured here. Ubiquitin is an interesting protein because it is localized in Lewy bodies, which are the pathologic hallmarks of PD. Ubiquitin is a small covalent modifier that forms a polyubiquitin chain on proteins. The polyubiquitin chain, which becomes a degradation signal for proteasome or lysosomal degradation or a signal for other processes, is synthesized by a cascade reaction involving the 3 enzymes ubiquitin-activating enzyme, ubiquitin-conjugating enzyme, and ubiquitin-ligating enzyme, which act as substrate-recognition molecules. We showed that (*a*) parkin has ubiquitin ligase activity with UbcH7, (*b*) the mutations in parkin that cause PD cause a loss of its ubiquitin ligase activity, and (*c*) proteasome inhibition leads to an accumulation of unknown parkin substrates in SH-SY5Y cells, indicating that the part of parkin linked to ubiquitination is a recognition signal for proteasomal degradation. Thus, our *Nature Genetics* article presented the important finding that impairment in the protein-degradation system causes dopaminergic cell death in PD. We speculated that substrates of parkin accumulate in parkin-deficient brains because of insufficient ubiquitination by mutant parkin. The accumulation of substrates may cause neuronal death in PD. We also suggested that unknown substrates of parkin might play important roles in PD pathogenesis.

To date, >100 parkin mutations have been identified. Various reported substrates of parkin include CDC-rel-1, *O*-glycosylated α-synuclein, the parkin-associated endothelin-like receptor, the α-synuclein–binding protein synphilin-1, actin filaments, the poly(Q)-expanded mutant of ataxin-3, Huntington disease polyglutamine proteins, the amyloidogenic Alzheimer disease Aβ 1–42 peptide (amyloid-β peptide 1–42), and aβ-tubulin. In support of these findings, parkin-linked animal models have shown a dysregulation of dopaminergic cells. Additionally, parkin activity is decreased in sporadic PD. Parkin is considered to play an important role in familial PD and other neurodegenerative disorders. Parkin is a broad neuroprotective agent that acts against a wide range of toxic insults, including those that are not part of the ubiquitin-proteasome system. Parkin also associates with mitochondrial membranes and interacts with the phosphatase and tensin homolog–induced putative kinase gene to protect mitochondrial function. Clarifying the relationships between parkin, ubiquitination, and mitochondria may provide insights into PD pathogenesis.

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[5] This article has been cited more than 950 times since publication.
[6] Nonstandard abbreviations: PD, Parkinson disease; Aβ 1–42 peptide, amyloid-β peptide 1–42.
[7] Human genes: *PARK2*, parkinson protein 2, E3 ubiquitin protein ligase (parkin).

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REVIEW

# Molecular pathogenesis of Parkinson's disease: update

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## ABSTRACT

Parkinson disease (PD) is a neurodegenerative disease characterised by progressive disturbances in motor, autonomic and psychiatric functions. Much has been learnt since the disease entity was established in 1817. Although there are well established treatments that can alleviate the symptoms of PD, a pressing need exists to improve our understanding of the pathogenesis to enable development of disease modifying treatments. Ten responsible genes for PD have been identified and recent progress in molecular research on the protein functions of the genes provides new insights into the pathogenesis of hereditary as well as sporadic PD. Also, genome wide association studies, a powerful approach to identify weak effects of common genetic variants in common diseases, have identified a number of new possible PD associated genes, including PD genes previously detected. However, there is still much to learn about the interactions of the gene products, and important insights may come from chemical and genetic screens. In this review, an overview is provided of the molecular pathogenesis and genetics of PD, focusing particularly on the functions of the PD related gene products with marked research progress.

## INTRODUCTION

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease, named after James Parkinson's who provided a classic account of the condition in 1817. Affecting 1–2% of the population over the age of 65 years, the prevalence of PD increases by approximately 4% in those older than 85 years. Ten genes that contribute to the genetic aetiology of hereditary PD (hPD) were identified, mainly through positional cloning strategies in inherited PD patients and families (table 1).[1 2] Several responsible genes for hPD have been identified, and based on functional studies in vitro and in vivo of gene products, some have been found to interact with each other in various cellular systems for homeostasis, such as synaptic homeostasis (α-synuclein), mitochondrial maintenance (PINK1, parkin, DJ-1, Omi/HtrA2), autophagy–lysosome pathway (α-synuclein, parkin, PINK1, Omi/HtrA2), axonal transport (LRRK2) and ubiquitin proteasome systems (α-synuclein, parkin, DJ-1, UCH-L1). Impairments in a number of cellular systems have been suggested to underlie hPD (figure 1). Also, more recent studies revealed that mutations in the same genes can be involved in familial PD and be risk factors for sporadic PD (sPD), suggesting that inherited and sPD could have common pathological mechanisms.[3] Therefore, understanding the function of the proteins encoded by hPD genes will hopefully further our understanding of the mechanisms leading to inherited and sPD.

In this review, we will summarise the latest research progress in the molecular mechanisms of hPD and genetic association studies of sPD.

## HEREDITARY PD

### α-Synuclein (PARK1 and PARK4)

#### Clinicogenetics

*SNCA* was the first causal PD gene identified in a large Italian family.[4] Mutations (A30P, E46K and A53T), duplications and triplications of the *SNCA* gene have been reported.[2] Clinical features of patients with the E46K mutation are similar to those of dementia with Lewy bodies, while A30P is not associated with severe dementia. Individuals with *SNCA* triplication developed an early onset form of PD with rapid progression and more extended neurodegeneration.[5]

Recent genome wide association studies (GWAS) have demonstrated a strong association between common single nucleotide polymorphism within the *SNCA* locus and PD in European and Japanese population, consistent with the finding that variation at the *SNCA* locus increases PD susceptibility.[6–9] Although the *SNCA* single nucleotide polymorphism associated with sPD show a low OR (1.2–1.4), these findings are consistent with α-synuclein aggregation pathology.

#### Molecular biology

α-Synuclein is mainly expressed in the presynaptic terminal of the CNS. The protein binds with lipids and unfolds in the steady state. Although the exact function remains unclear, it regulates dopamine homeostasis in presynaptic vesicle cycling.[5] The phenotype of α-synuclein knockout mice is unremarkable and only shows a mild decrease in dopamine levels in the striatum and a mild decrease in synaptic vesicles in the hippocampus. Compared with the wild-type α-synuclein, mutant forms easily aggregate in neuronal cells in vitro and in vivo.[10 11] Transgenic mice with wild or mutant α-synuclein under various promoters have shown neuronal inclusions, mitochondrial abnormalities and neurodegeneration.[12–14] Which type of α-synuclein species is the most toxic to cells remains unclear but some studies assert that mature aggregates are not themselves the toxic moiety but rather an attempt by the cell to clear small toxic oligomers.[15] Hsp90 modulates the assembly of α-synuclein in an ATP

**Table 1** Genetic and clinical characteristics of hereditary Parkinson's disease

| Locus | Inheritance | Gene | Type of mutation | Clinical features |
|---|---|---|---|---|
| PARK1/PARK4 | AD | SNCA | Missense, duplication, triplication | A30P: late onset, L-dopa responded parkinsonism; A53T: typical parkinsonism with rapid progression; E64K: DLB-like symptoms; duplication: typical parkinsonism; triplication: early onset parkinsonism with rapid progression |
| PARK2 | AR | PRKN | Nonsense, frameshift, missense | Early onset, symmetric, slowly progressed parkinsonism with spasticity and sleep benefits |
| PARK3 | AD | Unknown | – | – |
| PARK5 | AD | UCH-L1 | Missense | Similar to sporadic PD |
| PARK6 | AR | PINK1 | Nonsense, frameshift, missense | Early onset typical parkinsonism with psychiatric symptoms and L-dopa associated dyskinesia |
| PARK7 | AR | DJ-1 | Missense | Early onset parkinsonism with psychiatric symptoms, occasionally with scoliosis and blephalospasm |
| PARK8 | AD | LRRK2 | Missense | Middle to late onset typical parkinsonism with response to L-dopa |
| PARK9 | AR | ATP13A2 | Missense, deletion, insertion, duplication | Rapidly progressed parkinsonism with dementia and pyramidal features |
| PARK10 | Sporadic | Unknown | – | – |
| PARK11 | AD | Unknown | – | – |
| PARK12 | Sporadic | Unknown | – | – |
| PARK13 | AD | Omi/HtrA2 | Missense | Typical parkinsonism |
| PARK14 | AR | PLA2G6 | Missense | Early onset parkinsonism with rapid progression, cognitive decline and brain atrophy (cerebellum and cerebrum) |
| PARK15 | AR | FBXO7 | Missense, frameshift | Early onset parkinsonism with spasticity and response to L-dopa |
| PARK16 | Sporadic | Unknown | – | – |

AD, autosomal dominant; AR, autosomal recessive; DLB, dementia with Lewy bodies; PD, Parkinson's disease.

dependent manner by restricting conformational fluctuations of α-synuclein.[16] Recent advances in research on the protein degradation system associated with PD revealed the importance of ubiquitin proteasome and the autophagy–lysosome pathway in disease pathogenesis.[17] Wild-type α-synuclein is degraded by both chaperone mediated autophagy and macroautophagy, while A30P and A53T are degraded mainly by the latter.[17–19] Furthermore, macroautophagy itself is blocked by α-synuclein via Rap1a dysregulation.[20]

Several lines of evidence have shown that permeabilised α-synuclein from a neuron may be toxic to neurons and/or glias they are next to. Actually, grafted healthy neurons can gradually develop the same pathology as host neurons in PD brains.[21] These findings have suggested that non-cell autonomous cell death as well as cell autonomous cell death may have an important role in disease pathogenesis.

## Parkin (PARK2)

### Clinicogenetics

The first genetic locus for autosomal recessive juvenile parkinsonism was mapped to chromosome 6, and the disease gene named parkin (*PRKN*) was identified in consanguineous families.[22–24] Mutations in the *PRKN* gene are most common in autosomal recessive juvenile parkinsonism and many mutations have been reported.[3] The clinical picture is similar to that of sPD except for earlier onset, dystonic features, brisk reflexes and sleep benefit. Pathologically, no Lewy bodies were seen in most cases.[25–27] Whether or not heterozygous *PRKN* mutations may cause or increase the susceptibility to late onset typical PD remains controversial. [18F]Fluorodopa uptake by positron emission tomography was reduced in heterozygous carriers without symptoms.[28 29] In addition, heterozygous carriers of *PRKN* mutations have been reported to have either minor motor signs or present with late onset parkinsonism, suggesting a link between heterozygous mutations and disease pathogenesis.[27 30 31] On the other hand, screening for *PRKN* mutations in late onset PD and healthy controls revealed similar frequencies of genetic variants.[32 33]

### Molecular biology

Parkin is associated with the ubiquitin proteasome system as an E3 ubiquitin ligase.[34] The C terminal binds with ubiquitin E2 enzymes and recognises a substrate whereas the N terminal interacts with the 19S subunit of proteasome. A nonsense mutation lacking the rear RING finger motif had no E3 activity and sole IBR-RING2 retained E3 activity, and thus most parkin mutations do not lead to loss of kinase activity.[35] α-Synuclein and synphilin-1 were identified as parkin substrates and consist of Lewy bodies.[36 37] Parkin mainly localises in the cytoplasm as well as in plasma membranes and partly in mitochondria. Under physiological or pathological conditions, parkin is involved in mitochondrial maintenance and recent evidence revealed that parkin with PINK1 physically associate and functionally cooperate to identify and label damaged mitochondria for selective degradation via autophagy (mitophagy).[38–42] Protein–protein interactions between parkin and other PD related genes are detailed in each gene section.

## PINK1 (PARK6)

### Clinicogenetics

PARK6 was first identified on chromosome 1p36.[43] The disease gene was identified as *PINK1* (PTEN induced kinase 1) containing eight exons.[44] The clinical characteristics are autosomal recessive, early onset, slow disease progression and L-dopa responsive parkinsonism. Most mutations were missense mutations, but whole gene deletions were also reported.[45 46] Many putative pathogenic mutations were also observed in a heterozygous state in familial and sPD patients as well as in healthy controls. However, most of the studies have not checked the copy number variants, causing the mutation pathogenicity to remain controversial.[2] Lewy bodies, neuronal loss and astrocytic gliosis in the substantia nigra were detected in a patient with *PINK1* compound heterozygous mutations.[47]

### Molecular biology

PINK1 has eight exons encoding 581 amino acids, including a mitochondrial targeting sequence, transmembrane domain and

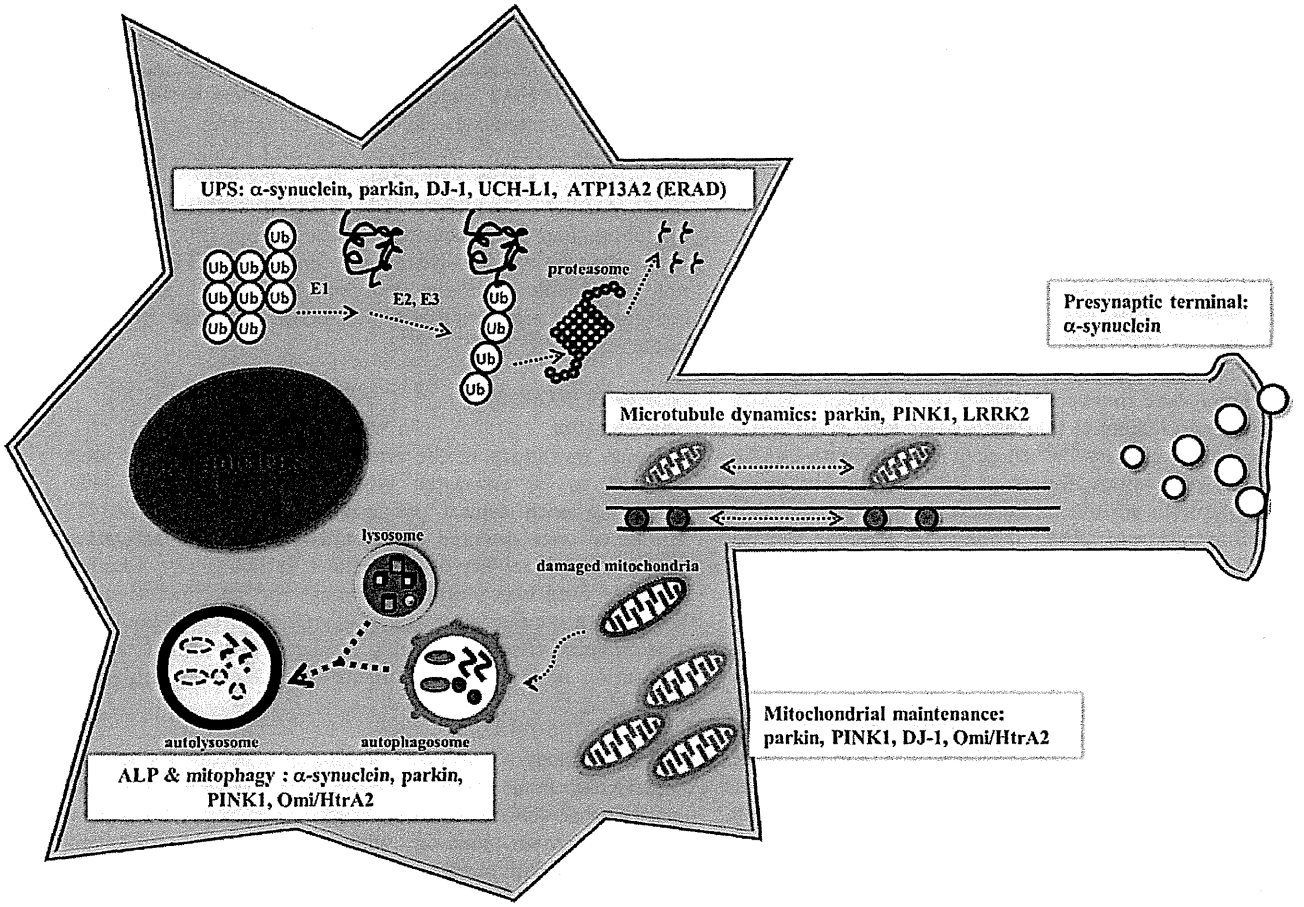


**Figure 1** Schematic representation of the possible pathogenesis in hereditary Parkinson's disease. ALP, autophagy—lysosome pathway; ERAD, endoplasmic reticulum associated degradation; Ub, ubiquitin; UPS, ubiquitin proteasome system.

kinase domain.[48] The gene product is ubiquitously expressed in the brain and systemic organs. The protein mainly localises in mitochondria, especially in the outer membrane. PINK1 is a serine—threonine kinase and several pathological mutations in PINK1 have been reported to change their kinase activities.[49–52] In addition, Rictor (a component of mTORC2),[53] tumour necrosis factor receptor associated protein 1 (TRAP1; a mitochondrial chaperone),[50] Omi (PARK13 gene product) and parkin (PARK2 gene product) were identified as substrates for PINK1.[54 55]

PINK1 regulates mitochondrial dynamics and respiratory functions.[38 53 56–58] Mitochondrial fission is accelerated by PINK1 overexpression accompanied by parkin.[59 60] PINK1 ablation with siRNA in neurons reduces resistance against oxidative stress while its overexpression provides resistance.[61] Using genetically modified Drosophila models, we see that PINK1 deficiency causes the same phenotype as parkin deficiency and the PINK1 deficiency phenotype is rescued by parkin complementation, suggesting that parkin is downstream of PINK1.[62–64] Several lines of evidence have provided new aspects of the PINK1/parkin pathway associated with mitochondrial elimination via macroautophagy (mitophagy). When mitochondrial membrane potentials are lost, endogenous PINK1 is accumulated followed by parkin recruitment, and subsequently the depolarised mitochondria were eliminated by mitophagy.[40 41 65 66] Mitochondrial targeting sequence, kinase activity of PINK1 and the linker domain of parkin are indispensable for the PINK1/parkin mediated mitophagy.

## DJ-1 (PARK7)

### Clinicogenetics

Clinical features of *PARK7* are characterised by early onset parkinsonism with scoliosis, blephalospasm and psychiatric symptoms, similar to those of *PARK2* and *PARK6*. The disease gene was identified as *DJ-1*, which has eight exons encoding 189 amino acids. Three missense mutations (L166P, M26I, E64D) in exons 1—5 of the gene have been identified in Italian, Dutch and Uruguayan families. *DJ-1* protein was detected around Lewy bodies, suggesting *DJ-1* is not in the main structure of Lewy bodies. However, the protein was detected in astrocytes and in a part of the cytoplasmic inclusions positive to tau in brains with corticobasal degeneration, progressive supranuclear palsy and multiple system atrophy.[67–69]

### Molecular biology

DJ-1 is almost ubiquitously expressed in organs, including the brain. Endogenous DJ-1 is present in synaptic terminals, mitochondria and membranous organelles.[70 71] DJ-1 with the L166P mutation lost more stability compared with the wild-type and mutant DJ-1 (M26I, E64D).[72] In DJ-1 knockout mice, no significant loss of dopaminergic neurons and decreased susceptibility to oxidative stress were noted.[73] DJ-1 is a multifunctional redox sensitive protein regulating mitochondrial oxidative stress and increases expression levels of SOD1 in an Erk1/2-Elk1 pathway dependent manner,[74] and facilitates prosurvival factor Akt, leading to suppression of apoptosis.[75] Also, the protein

inhibits TRAIL induced apoptosis by blocking Fas associated protein death domain mediated pro-caspase-8 activation.[76] Along with parkin and PINK1, DJ-1 has various cellular functions such as regulation of mitochondrial morphology as well as misfolded protein degradation by forming an E3 ligase complex with those proteins.[77]

## LRRK2 (PARK8)

### Clinicogenetics

Clinical features of PARK8 are essentially similar to those of sPD except for earlier onset age. The disease gene was identified as the leucine rich repeat kinase 2 gene (*LRRK2*) linked to autosomal dominant inherited PD encoding 2517 amino acids.[78–80] PARK8 is the most common form of hPD in the world. Until now, 20 missense or nonsense mutations have been reported.[81] *LRRK2* mutations were also found in some sPD cases; neuropathological findings were heterogeneous.[82 83] Most of the cases with *LRRK2* mutations showed various degrees of Lewy bodies but intraneuronal aggregations positive to tau were rarely detected.[79 84 85] The G2019S mutation in *LRRK2* is the most common genetic cause of PD, accounting for a significant proportion of both autosomal dominant and sPD cases.

### Molecular biology

LRRK2 protein, containing a GTPase domain, a Ras of complex domain, a C terminal of Ras complex domain and a mitogen activated kinase domain, is highly expressed in the brain, and mRNA levels are rich in the striatum and hippocampus compared with other regions.[86] Intracellular LRRK2 is mainly distributed in the plasma membrane and vesicular structures.[87 88] Immunoprecipitation techniques have revealed that LRRK2 interacts with parkin.[89] In transgenic flies, neurodegeneration by LRRK2 with or without a mutation is modified by overexpression or siRNA knockdown of parkin, PINK1 or DJ-1, suggesting genetic interaction between them.[90 91] Activity changes of LRRK2 kinase and GTPase have been suspected as a key factor in LRRK pathogenesis. Changes in LRRK2 activity cause alterations in mitogen activated protein kinase, translational control, tumour necrosis factor $\alpha$/Fas ligand and Wnt signalling pathways with the cell biological functions of LRRK2 such as vesicle trafficking.[80] The most common pathological mutation in LRRK2, G2019S LRRK2, causes neurite retraction by activation of Rac1 small GTPase.[92] LRRK2 mutations inhibit an endogenous peroxidase by phosphorylation promoting dysregulation of mitochondrial function and oxidative damage.[93] G2019S human LRRK2 transgenic rat models specifically expressed in the nigrostriatal system have shown progressive degeneration of nigral dopaminergic neurons.[94] In terms of LRRK2 control, PKA has been identified as a potential upstream kinase of LRRK2 at S935, on which binding of 14-3-3 with LRRK2 depends.[95] However, the exact biological function of LRRK2 remains largely unclear because no physiological substrates have been identified to date.

## ATP13A2 (PARK9)

### Clinicogenetics

PARK9, also known as Kufor–Rakeb syndrome, is an autosomal recessive parkinsonian disorder characterised by early onset (14–16 years old), good response to L-dopa treatment, pyramidal feature, supranuclear gaze palsy and dementia.[96] The gene locus was mapped to 1p36 and the disease gene was identified as *ATP13A2*, which localises in lysosomal membranes.[97] Various types of mutations in the *ATP13A2* have been reported.

### Molecular biology

ATP13A2 is predicted to be a lysosomal P5-type ATPase that plays important roles in regulating cation homeostasis. Although ATP13A2 function remains unclear, it might be involved in protecting cells against manganese and mutant $\alpha$-synuclein toxicity.[98] Wild-type ATP13A2 localises mainly in lysosomes whereas three separate mutants with a mutation involved in PD cause retention of the protein in the endoplasmic reticulum, and are eliminated by the endoplasmic reticulum associated degradation pathway.[99] Wild-type ATP13A2, but not pathogenic mutants, reduced intracellular manganese concentration and prevented cytochrome C release from the mitochondria.[100]

## Omi/HtrA2 (PARK13)

### Clinicogenetics

Missense mutations in the gene coding for Omi/HtrA2 were reported to be associated with four patients with sPD, presenting with typical parkinsonism.[55] G399S and A141S mutations were detected and resulted in defective activation of the protease activity of Omi/HtrA2. Pathologically, accumulation of Omi was found in neuronal and glial inclusions in brains with $\alpha$-synucleinopathies as well as in Lewy bodies.[101] The largest association study revealed no overall strong association of Omi/HtrA2 variants with sPD in populations worldwide.[102]

### Molecular biology

Omi/HtrA2 is a nuclearly encoded mitochondrial protein consisting of 458 amino acids, originally identified as a proapoptotic protein binding with an apoptosis inhibiting protein.[103 104] Omi knockout mice presented with neuronal loss in the striatum and died within 30 days of birth.[105] Cells overexpressing Omi mutant with G399S have shown mitochondrial morphological changes followed by dysfunction and increased susceptibility against oxidative stress.[55] Interestingly, wild-type Omi/HtrA2, not protease defective mutant, activates autophagy through digestion of Hax-1, a Bcl-2 family related protein that represses autophagy via Beclin-1 inhibition, suggesting an insufficient protein degradation system may play a key role.[106]

## PLA2G6 (PARK14)

### Clinicogenetics

PARK14 is an autosomal recessive parkinsonian syndrome characterised by early onset rapidly progressive parkinsonism, dystonia, cognitive decline, and cerebral and cerebellar atrophy. Through homozygosity mapping and direct sequencing, two different homozygous mutations in *PLA2G6*, which also causes infantile neuroaxonal dystrophy and neurodegeneration with brain iron accumulation, were identified.[107 108] Cranial MRI did not detect iron accumulation in the basal ganglia in most cases with this disorder.[108 109]

### Molecular biology

The PLA2G6 gene encodes a group VIA calcium independent phospholipase A2, also known as calcium independent phospholipase A2 $\beta$, which hydrolyses the sn-2 acyl chain of phospholipids, generating free fatty acids and lysophospholipids. In an in vitro assay, wild-type PLA2G6 associated with infantile neuroaxonal dystrophy/neurodegeneration with brain iron accumulation failed to catalyse fatty acid release from phospholipids, while PARK14 associated mutations ((R741Q, R747W and R632W) did not, implying that other functions of PLA2G6

include interactions with calmodulin and that PLA2G6 might also be associated with calcium/calmodulin dependent protein kinase II-β.[110 111]

### FBXO7 (PARK15)

#### Clinicogenetics

Only three families with mutations in *FBXO7* have been reported.[112 113] Affected individuals had juvenile onset (10–19 years old) of progressive parkinsonism associated with spasticity, and variable response to L-dopa. No pathological studies have been reported.

#### *Molecular biology*

Fbox7 is a member of the F box containing protein (FBP) family with an F box domain. F box containing proteins are expected to function as molecular scaffolds in the formation of the protein complex; however, the exact function of FBXO7 remains unclear.

## OTHER GENES ASSOCIATED WITH PARKINSON'S DISEASE

GWAS have uncovered a number of candidate genes involved in PD in European and Japanese populations, indicating a substantial contribution of genetics underlying susceptibility to both early onset and late onset PD.[6 7 114–119] These studies have shown repeatedly a common variation in *SNCA* and an inversion of the region containing the *MAPT*. Recent genetic studies revealed mutations in the *GBA* gene, the most widespread genetic risk factor for parkinsonism identified to date.[120–124] In this section, we summarise the molecular mechanisms of the two genes, MAPT and GBA.

### MAPT

Mutations in *MAPT*, encoding microtubule associated tau, result in tauopathies, including progressive supuranuclear palsy, corticobasal degeneration and frontotemporal lobar degeneration.[125] Tau is a soluble protein, but insoluble aggregates are produced during the formation of neurofibrillary tangles which disrupts microtubule associated dynamics and neuronal functions. Considering the interplay between α-synuclein and tau reported previously,[126] it is interesting that there would be a common pathogenesis associated with aggregation formations.

### GBA

Early observed patients with Gaucher disease and their heterozygous relatives present with parkinsonism.[127] In addition, autopsy studies have shown the presence of mutant glucocerebrosidase (GCase) in α-synuclein positive Lewy bodies in Gaucher disease patients and carriers with α-synucleinopathies.[128] GCase is a lysosomal hydrolase with 497 amino acids that catalyses the metabolism of the glycolipid glucosylceramide to ceramide and glucose. Cells overexpressing mutant GCase promoted α-synuclein accumulation in a dose and time dependent manner.[129] α-Synuclein GCase interacts selectively under lysosomal solution conditions (pH 5.5) and the interaction site was mapped to the α-synuclein C terminal residues 118–137.[130] Insufficient functions of the lysosomes may have an effect on chaperone mediated autophagy or macroautophagy.

## CONCLUDING REMARKS

In the 14 years since the first causative gene (α-synuclein) in PD was discovered, great advances have been made in understanding the biology of the disease. Recent evidence shows that the environment plays no role in the aetiology of PD.[131] In addition, GWAS suggest that a number of genes influence susceptibility.[3] The PD associated genes provide valuable clues regarding the molecular pathogenesis of PD because the pathomechanism for sPD would have certain pathways in common with those of hPD. Importantly, basic biological studies in PD have led to numerous potential therapeutic strategies. For example, a specific inhibitor for LRRK2 phosphorylations at Ser910 and Ser935 was recently developed.[132] In the future, it becomes more important to translate laboratory data, including molecular pathogenesis as well as genetic associations, into clinical treatments, leading to disease modifying therapies to conquer the disease onset and/or progression.

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# Molecular pathogenesis of Parkinson's disease: update

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# Autosomal dominant Parkinsonism: its etiologies and differential diagnoses

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SUMMARY

Recently, several genes for parkinsonism have been identified. Among them, familial Parkinson's disease (PD) could be assigned for PARK disorders. PARK disorders consist of three different inherited modes such as autosomal recessive, autosomal dominant modes and susceptible genes. Some of them manifest not only typical parkinsonism, but also dystonia, pyramidal sign, and mental dysfunctions. While the monogenic forms of PARK disorders have been reviewed extensively, it is not easy to do differential diagnosis of PARK disorders due to the additional features except for typical parkinsonism. In this presentation, we focus on two different scenarios of patients with autosomal dominant parkinsonism: (1) parkinsonism with mutations in one of the PARK genes; (2) parkinsonism with mutations other than PARK genes or yet other genes where parkinsonism is a well recognized, concomitant, or even an isolated feature.



## 1. Introduction

In the past decade, a number of PARK disorders have been identified (Table 1). At the present time, 18 loci have been detected so far, and among them, there have been eleven identified genes. *SNCA* and *Lrrk2* have been recognized as major causative genes for autosomal dominant PD in which clinical symptoms are very similar to those of the sporadic form of PD [1]. Moreover, genome wide association studies revealed that polymorphisms in the same genes such as *SNCA* and *Lrrk2* could be involved in sporadic PD as one of risk factors, suggesting that inherited form and sporadic PD could share a common pathway. Therefore, understanding the function of these gene products encoded by both genes will hopefully elucidate the mechanisms leading to nigral degeneration. In addition, *GIGYF2* (*Grb10-Interacting GYF Protein-2* gene) responsible for PARK11 and *Omi/HtrA2* for PARK13 are causative genes for low frequent autosomal dominant PD.

Considering the mode of inheritance, autosomal dominant parkinsonism could be caused by toxic-gain of function. In addition to PARK disorders, there has been typical parkinsonism without PARK genes such as DYT or SCA genes. In contrast, there has been atypical parkinsonism in other genetic disorders typically characterized by features other than parkinsonism. Moreover, glucocerebrosidase (GBA), the gene responsible for Gaucher's disease, is one of the susceptible genes that poses a risk for developing into PD even in heterozygous cases. As it is difficult to differentiate various types of autosomal dominant parkinsonism, it is important to understand the phenotype–genotype. In addition, there appears to be a similarity in the pathogenesis between sporadic and familial PD. This finding provides us a good hint to clarify a mechanism of nigral degeneration between the sporadic and monogenic form of PD [2]. In this review, we summarize the phenotype–genotype correlation and the possible role of gene products.

## 2. Autosomal dominant parkinsonism as PARK disorders

Among PARK disorders, PARK8 is the most frequent autosomal dominant disorder. In contrast, although the frequency of SNCA mutations including missense or multiplications have been much lower than that of PARK8 disorders, the role of this gene product is essential for the formation of Lewy bodies and neuritis. Thus, both genes are major genes for autosomal dominant PD [3]. In addition, PARK5, 11, and 13 have been reported as PARK disorders. Regarding PARK5, only one family has been reported so far. Therefore, it is not clear whether or not this is a responsible gene, UCH-L1 is the true causative gene for PARK5. Also, PARK11-linked PD has been linked to 2q36–37. Subsequently, mutations in *GIGYF2* (*Grb10-Interacting GYF Protein-2* gene) were found in Italians and French. However, extensive studies failed to detect the same mutations in patients with familial PD, and the same mutations have been found in normal controls, suggesting that it seems to be unlikely that *GIGYF2* is the causative gene for PARK11.

Missense mutations in Omi/HtrA2 were reported to be associated with four patients with the sporadic form of PD, presenting typical parkinsonism. G399S and A141S mutations were detected and resulted in defective activation of the protease activity of Omi/HtrA2. Pathologically, accumulation of Omi was found in neuronal and glial inclusions in brains with alpha-synucleinopathies as well as in Lewy bodies. The largest association study revealed no overall strong association of Omi/HtrA2 variants with PD in populations worldwide [4].

*SNCA* and *Lrrk2* are major causative genes for autosomal dominant PD. *SNCA* was the first causal PD gene identified in a

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**Table 1**
Genetic and clinical characteristics of the hereditary Parkinsonism (Mainly autosomal dominant forms of pakinsonism) (see text)

| Locus | Inheritance | Gene | Tape of mutations | Clinical features |
|---|---|---|---|---|
| PARK1/PARK4 | AD | *SNCA* | Missense, duplication, triplication | A30P: late-onset, Levodopa responded parkinsonism, PD; A53T: typical parkinsonism with rapid progression. PD; E64K: DLB-like symptom; duplication: typical PD; triplication: early-onset PD with rapid progression |
| PARK3 | AD | *unknown* | – | – |
| PARK5 | AD | *UCH-L1* | missense | Typical PD, only one family |
| PARK8 | AD | *LRRK2* | missense | Middle-to-late onset typical PD with response to Levodopa |
| PARK11 | AD | *GIGYF2?* | missense | Typical PD? |
| PARK13 | AD | *Omi/HtrA2* | missense | Typical PD |
| DYT3 | XR | *TAF1* | missense | Parkinsonism, dystonia |
| DYT5 | AD | *GCH1* | missense | Dopa responsive dystonia |
| DYT12 | AD | *ATP1A3* | missense | Orofacial dystonia, dysarthria, dysphagia, involuntary dystonic spasms, parkinsonism with bradykinesia and postural instability |
| SCA2 | AD | *Ataxin 2* | CAG repeat | Levodopa responsive parkinsonism of patients of Asian origin |
| SCA3 | AD | *Ataxin 3* | CAG repeat | levodopa responsive parkinsonism |
| SCA8 | AD | *Ataxin 8*<br>*Ataxin 8 opposite strand* | CTA/CTG repeat | Atypical parkinsonism |
| SCA17 | AD | *TBP* | CAG repeat | Atypical parkinsonism |
| POLG | AD | *POLG* | missense | Atypical parkinsonism and external ophthalmoplegia |
| GBA | AD or AR | *GBA* | missense | Early onset parkinsonism or typical PD, similar to sporadic PD |

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive; DLB, dementia with Lewy bodies; PD, Parkinson.

large Italian family. Three missense mutations (A30P, E46K and A53T), duplications and triplications of the *SNCA* gene have been reported [5]. In Japanese patients with familial PD, duplication is the most frequent type among *SNCA* mutations. No missense mutation has been identified so far. Clinical features of patients with E46K mutation are similar to those of dementia with Lewy bodies, whilst A30P is not associated with severe dementia. Individuals with *SNCA* triplication developed an early-onset form of PD with rapid progression and more extended neurodegeneration [6].

The recent genome-wide association studies (GWAS) have demonstrated a strong association between common single nucleotide polymorphism (SNPs) within the *SNCA* locus and the disease in different populations, consistent with the finding that variation at the *SNCA* locus increases PD susceptibility [6,7]. Very interestingly, no SNPs have been reported so far within the coding region of the gene, suggesting that this gene may be a new gene considering the evolution of human genome.

Alpha-synuclein is mainly expressed in the presynaptic terminal of the central nervous system and a major component of Lewy bodies. The protein binds with lipids and unfolds in the steady state. Although the exact function remains unclear, it regulates dopamine homeostasis in presynaptic vesicle cycling. Compared to the wild-type alpha-synuclein, mutant forms easily aggregate in neuronal cells *in vitro* and *in vivo* [8,9]. What types of alpha-synuclein species are the most toxic to cells remains unclear, but some studies assert that mature aggregates are not themselves the toxic moiety rather an attempt by the cell to clear small toxic oligomers [10]. Recent advances in the protein degradation system in PD reveal the importance of both ubiquitin proteasome (UPS) and autophagy-lysosome pathway (ALP) in the disease pathogenesis [11]. Wild-type alpha-synuclein is degraded by both chaperone-mediated autophagy (CMA) and macroautophagy, whilst A30P and A53T is mainly the latter.

Several lines of evidence have shown that permeabilized alpha-synuclein from a neuron may be toxic to neurons and/or glias. Actually, grafted healthy neurons can gradually develop the same pathology as host neurons in the PD brains [12]. These findings have suggested that non-autonomous cell death as well as cell autonomous cell death may play an important role on the disease pathogenesis as well in Amyotrophic lateral sclerosis (ALS).

PARK8 is the most common form of hereditary PD in the world. The original family was described in a Japanese journal by Nukada et al. in 1978. Clinical features of PARK8 are essentially similar to those of sporadic PD. The locus was mapped to the centromeric region of chromosome 12 (12p11.23–q13.11) and the disease gene was identified as the leucine-rich repeat kinase 2 gene (*LRRK2*). Until now, 20 missense or nonsense mutations have been reported [13]. G2019S is the most common missense mutation seen in European countries, Ashkenazi Jewish people, and Arabic subjects in North Africa. I2020T mutation was found in the original family in Sagamihara. Neuropathological findings were heterogenous [14–16]. Most of the cases with *LRRK2* mutations showed various degrees of Lewy bodies, but intraneuronal aggregations positive to tau were rarely detected.

LRRK2 protein, containing GTPase domain, Ras-of-complex (ROC) domain, a C-terminal of Ras complex (COR) domain and mitogen-activated kinase domain, is highly expressed in brain, and the levels of mRNA are rich in the striatum and hippocampus compared to other regions. Intracellular LRRK2 mainly distributes in the plasma membrane. However, LRRK2 proteins are also present in membranous organelles including ER, golgi apparatus, early endosomes, lysosomes, synaptic vesicles, and mitochondria. Moreover, it has been reported that LRRK2 binds to lipid rafts within the synaptosomes [17].

Changes in LRRK2 activity cause alterations in mitogen-activated protein kinase, translational control, tumor necrosis factor alpha/Fas

ligand and Wnt signaling pathways with the cell biological functions of LRRK2 such as vesicle trafficking. The most common pathological mutation in LRRK2, G2019S LRRK2, causes neurite retraction by activation of Rac1 small GTPase. Thus, activity changes of LRRK2 kinase and GTPase may be involved as a key factor in the LRRK pathogenesis.

Among autosomal recessive PARK disorders such as PARK2, 6, and 7, single heterozygous mutations are known to have a parkinsonian phenotype. Thus, it would be possible that pseudo-autosomal dominant familial PD might take in place in some patients. This finding suggests that parkin, PINK1, and DJ-1 are also candidates for autosomal dominant parkinsonism.

## 3. Autosomal dominant parkinsonism without PARK genes

Clinical features associated with mutations of PARK disorders often markedly differ from those of classical parkinsonism. On the other hand, some gene-proven cases without PARK genes mimicking classical parkinsonism have been reported and the genes should thus be considered in the differential diagnosis of parkinsonism (Table 1). Dystonia plus parkinsonism should be considered for differential diagnosis. Currently, at least 20 monogenic forms of DYT disorders have been listed. Among them, DYT3, DYT5, and DYT12 present combined features, with dystonia and parkinsonism. Among three DYT disorders, only DYT12 is an autosomal dominant mode of inheritance. DYT12 is clinically characterized clinically characterized by orofacial dystonia, dysarthria, dysphagia, and involuntary dystonic spasms, predominantly in the upper limbs with superimposed parkinsonian features, primarily bradykinesia, and postural instability with or without rigidity [18]. The symptoms are not levodopa-responsive. DYT disorders usually lack responsiveness of levodopa except for DYT5.

Inherited ataxias represent a clinically and genetically heterogeneous group. Parkinsonism has been described in several of these. SCA2 mutations may cause classical, L-dopa-responsive parkinsonism in patients from different genetic backgrounds and seems to be particularly frequent among patients of Asian origin in whom it accounts for about 10% of familial parkinsonism [18]. Thus, clinicians should consider SCA2 for differential diagnosis in PD patients with autosomal dominant mode of inheritance and Asian origin. In addition, mutations of DNA Polymerase gamma (POLG) and the Twinkle genes are found in some patients presenting with predominant progressive external ophthalmoplegia (PEO) and concominant features of parkinsonism. Both are also causative genes for autosomal dominant PD.

Early identified patients with Gaucher disease (GD) and their heterozygous relatives present parkinsonism. In addition, autopsy studies revealed the presence of mutant glucocerebrosidase in alpha-synuclein positive Lewy bodies in GD patients and carriers with alpha-synucleinopathies [19]. Since then similar reports followed and heterozygous carriers of *GBA* were considered to have a high risk for sporadic PD. The age of onset of PD among *GBA* carriers was 39 to 65, disease duration 1.2 -16 years, and half of the patients had cognitive impairment. Recent meta-analysis revealed the OR of 5.43 for any mutation of *GBA* [20]. Thus *GBA* carriers have the highest risk for sporadic PD. It is interesting to speculate that lysosomal function is impaired in sporadic PD and GBA is a lysosomal enzyme. As there are many healthy carriers of GBA, some additional factors seem to be necessary to be afflicted with PD.

## 4. Conclusions

There are many diseases that have parkinsonism, which should be considered in the differential diagnosis (Table 1). It is important to evaluate the levodopa-responsiveness in the patients with autosomal dominant mode of inheritance based on the differential diagnosis.

## Conflict of interests

Nobutaka Hattori has received personal compensation for attending advisory board meetings as a member of the advisory boards of Boehringer Ingelheim and FP Pharmaceutical Company. He has received consultancy fees from Ohtsuka Pharmaceutical Company, Kyowa Hakko Kirin Pharmaceutical Company, GlaxoSmithKline, Novartis, and Schering-Plough.

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HISTORY

遺伝子工学からの恩恵 — 4

# 「iPS 細胞の誕生と再生医療への応用」

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Key words：　iPS 細胞，転写因子，再生医療

## Abstract

iPS 細胞は分化した体細胞に 4 つの転写因子（Oct3/4，Sox2，c-Myc，Klf4）を導入することで樹立される万能多能幹細胞である。2006 年に iPS 細胞は京都大学の山中教授らによって世界で初めて樹立され，動物マウス研究や ES 細胞研究とともに病態疾患メカニズムの解明や新しい治療法の確立，再生医療への応用が大きく期待されている。しかし，iPS 細胞の初期化のメカニズム，腫瘍化の危険性など取り組むべき課題は多く存在する。本稿では，主に現在までに報告されている研究成果を振り返るとともに臨床へ応用するために解決しなければならない問題などについての解説を行う。

## はじめに

1981 年にマウス胚性幹（Embryonic Stem: ES）細胞が発見され，分化多能性とほぼ無限な増殖能から再生医療への応用が大きく期待されたが，胚細胞を使用することから倫理的問題や法規制の問題などにより慎重な研究運用を求められた。1997 年には，体細胞クローン羊である“Dolly”が誕生し世界に大きな衝撃を与えた。Dolly 誕生により再生医療の新たな可能性が見いだされたが，残念ながら人への応用は技術面で難しく成功には至っていない。2006 年にマウス人工多能性幹細胞（induced Pluripotent Stem cell: iPS 細胞）の樹立に成功した。iPS 細胞は自己の細胞から樹立される万能多能幹細胞であることから倫理的な問題や免疫学的な拒絶反応がなく，再生医療への実用化にさらに大きく期待が集まるようになった。

## 1．iPS 細胞の誕生

1981 年にマウスの奇形腫を用いた早期胚から ES 細胞が発見され，1998 年にヒト由来 ES 細胞が報告された[1]。ES 細胞はほぼ全ての組織に分化する分化多能性を持ち，ほぼ無限に増殖可能であることから疾患病態メカニズムの解明，創薬研究，再生医療などへ応用が可能と考えられ注目されるようになった。しかし，ES 細胞は胚細胞を用いることから倫理的

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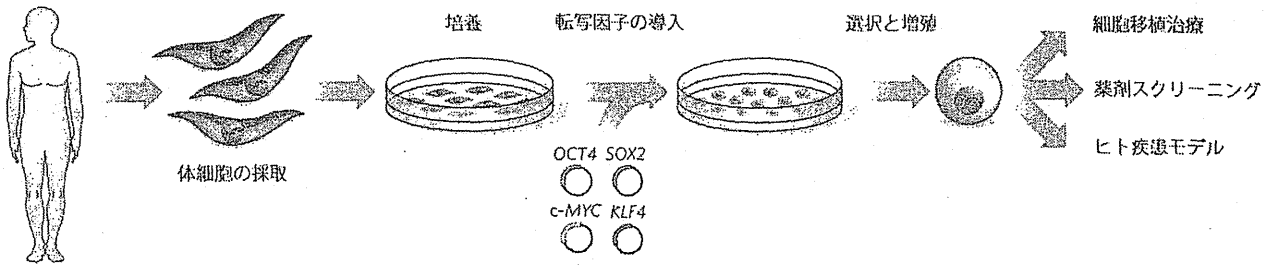


図　iPS 細胞樹立と活用法（文献 16 より改変）

表 1　iPS 細胞と ES 細胞の比較

| | iPS 細胞 | ES 細胞 |
|---|---|---|
| 利点 | 1.多能性<br>2.ほぼ無限な増殖能<br>3.胚細胞を用いない<br>4.免疫拒絶反応の可能性が低い | 1.多能性<br>2.ほぼ無限な増殖能<br>3.遺伝子導入が不要 |
| 欠点 | 1.遺伝子導入による癌化のリスク<br>2.初期化のメカニズムが不明 | 1.胚細胞の利用による倫理的問題<br>2.移植後の免疫拒絶反応の可能性<br>3.胚細胞が大量に必要 |

問題，法規制の問題などがあり慎重な研究運用を求められた。ES 細胞は移植細胞の腫瘍化や拒絶反応による生着率の低さなどの課題が多く，広く普及に至っていない。

2006 年 8 月に京都大学の山中教授らはマウスの皮膚から線維芽細胞を採取し，Oct3/4，Sox2，c-Myc，Klf4 の 4 つの転写因子（これらは山中因子と呼ばれている）をレトロウイルスベクターを用いて遺伝子導入することで体細胞の核をリプロミラミングし iPS 細胞の樹立に初めて成功した。2007 年 11 月には成人皮膚由来の線維芽細胞を用いてヒト iPS 細胞の樹立に成功した[2]（図）。iPS 細胞は形態学的，増殖能，表面抗原，遺伝子発現，エピジェネティック状態，テロメラーゼ活性などの点で ES 細胞と類似し，神経細胞や心筋細胞へ直接的に分化誘導することが可能である。特にヒト iPS 細胞は自己の細胞を用いて多能性幹細胞を樹立できることから ES 細胞が抱える倫理的問題や移植後の拒絶反応を回避することができるため，ES 細胞に替わり iPS 細胞が新たに注目を浴びるようになった（表 1）。

## 2．iPS 細胞の実用化と安全性

iPS 細胞樹立の発表以降，様々な体細胞や転写因子を用いて作製された iPS 細胞の樹立成功が報告されるようになった。現在，iPS 細胞は主に皮膚細胞，毛根組織，歯髄細胞，血液細胞から作製されるが，由来する細胞によって iPS 細胞の性質や能力に違いがみられることがわかってきている。iPS 細胞の実用化には均一で安定した性能が求められるため作製方法の標準化が求められている。当初，体細胞の初期化には山中因子が必須であることが明らかにされたが，iPS 細胞由来の細胞を

移植したキメラマウスの子孫の約20%に甲状腺癌や神経節芽細胞腫などの悪性腫瘍が形成されることが報告された[31]。腫瘍化は癌原遺伝子であるc-Mycの再活性化が原因と考えられ，c-Mycを除いたOct3/4，Sox2，Klf4でiPS細胞を作製できることが報告され，腫瘍形成はほぼ回避できている。また，Oct4，Sox2，Nanog，Lin28を用いる方法やOct4のみを用いる方法なども報告され，iPS細胞の作製方法については盛んに研究されている。現在は，初期化に必要な転写因子における役割や関連性などは完全には解明されていないが，Oct4が体細胞の初期化に最も重要であり，Sox2やKlf4はそれぞれSox1，Klf2，Klf5でも代用できることがわかってきている。

ところで，iPS細胞の腫瘍化の原因は転写因子だけではなく，遺伝子導入の際に用いるウイルスベクターの使用も一因と考えられている。そのため，ウイルスベクターを使用しないで導入する方法についても様々な研究が行われている。遺伝子工学で広く用いられるプラスミドベクターで導入された遺伝子の発現は一時的であるが，繰り返し遺伝子導入することでiPS細胞を作製できることが報告され，腫瘍化の危険性が低い点で有用と考えられている。その他にエピソーマルベクターやセンダイウイルス，ポリシストロニックベクターなどで遺伝子導入する方法や山中因子をコードするmRNAまたはこれにより合成されたタンパク質を細胞外から導入する方法などさまざま報告されている。

さらに，iPS細胞の作製効率の向上についても研究が進められている。山中因子での作製効率は数%であるが，c-Mycを用いない作製方法ではさらに効率が低下することがわかっている。c-Mycは作製効率に寄与する反面，腫瘍形成の可能性があるためc-Mycに替わる新しい転写因子が探索され，Mycファミリーの1つであるL-Mycが腫瘍化の危険性を上げずに効率良くiPS細胞を誘導できることが報告された[5]。また，iPS細胞誘導時に癌抑制遺伝子であるp53とその下流にあるp21が高く発現しリプロミングを阻害していることからp53を抑制する方法が報告された。その他に未授精卵や受精卵で高度に発現しているGli様転写因子Glis1をOct3/4，Sox2，Klf4とともに導入させる方法などさまざま報告されている。

表2　iPS細胞研究が行われている主な中枢神経疾患の一覧

| 中枢神経疾患 |
|---|
| 孤発性パーキンソン病 |
| 遺伝性パーキンソン病 |
| ハンチントン病 |
| 筋萎縮性側索硬化症 |
| 脊髄性筋萎縮症 |
| Friedreich失調症 |
| 家族性自律神経失調症 |
| Duchenne型筋ジストロフィー |
| Becker型筋ジストロフィー |
| Gaucher病 |
| Rett症候群 |
| Down症候群 |
| 脆弱X症候群 |
| Prader-Willi症候群 |

（文献16より）

このようにiPS細胞の実用化にはまだ解決すべき課題があるが，iPS細胞の安全性の向上に向けて初期化因子の選定，遺伝子導入方法，作製効率の改良など日進月歩で進められている。

## 3．iPS細胞を用いた研究

患者の体細胞から作製されたiPS細胞を用いることにより，希少疾患，遺伝性疾患，複数要因による疾患の病態メカニズムの解明や新たな治療方

法の開発が可能と考えられており，特に疾患モデルのない希少疾患では大きく期待されている。ここでは神経変性疾患に焦点を当てて紹介する。(表 2)

(1) 疾患特異的な iPS 細胞の作製と疾患研究

神経変性疾患にはさまざまな疾患が存在するが，いまだ疾患病態の詳細なメカニズムが解明されていないものが多く存在する。これまで報告されてきた剖検脳での病理所見は疾患の末期を反映したものであり，どのような過程で疾患が進行するかは不明な点が多い。患者の体細胞から作製された iPS 細胞は分化の過程から細胞変化を観察できることにより病態メカニズムの解明やさらには再生医療への応用が期待できる。現在までに多くの神経疾患モデル iPS 細胞が作製され研究が進められている[6]。

脊髄性筋委縮症 (Spinal Muscular Atrophy: SMA) や家族性自律神経失調症 (Familial Dysautonomia: FD) などの発症年齢の低い疾患は遺伝子要因が大きく，疾患モデル iPS 細胞の作製と疾患再現が早期に報告された。SMA では疾患 iPS 細胞由来の運動神経細胞が原因遺伝子の変異により細胞死を引き起こして神経細胞が減少し，FD では疾患モデル iPS 由来の神経堤細胞が原因遺伝子の転写異常により分化と遊走に異常が起こることが報告された[7,8]。どちらの疾患についても優れた動物モデルがなく，iPS 細胞を用いて病態を再現することで疾患病態の解明に大きな貢献をしている。

パーキンソン病 (Parkinson's Disease: PD) は振戦，無動，筋固縮，姿勢反射障害を主症状とする慢性進行性疾患である。PD のほとんどは孤発性であるが，一部は遺伝性であることから遺伝的要因と環境要因が複合的に関連していると想定されている。孤発型 PD 患者の皮膚線維芽細胞から作製された iPS 細胞を神経細胞に分化誘導させると，PD 患者由来の iPS 細胞と非 PD 患者由来の iPS 細胞のどちらも有意差がなかったことが報告され，孤発性 PD の発症には遺伝的要因よりも酸化ストレスや老化などの環境要因の方がより強い影響を及ぼしている可能性があることが示唆された[9]。一方で，PINK1 遺伝子異常をもつ PD 患者由来の iPS 細胞を神経細胞に分化誘導させるとミトコンドリアの parkin 蛋白の移行障害が確認されている[10]。さらには LRRK2 遺伝子異常をもつ PD 患者由来の iPS 細胞を神経細胞に分化誘導させ酸化ストレスである過酸化水素や 6-OHDA に暴露させると対照群に比べ神経細胞における酸化ストレス反応の上昇やαシヌクレインの増加が確認され，*in vitro* や *in vivo* で報告されている病態と同様な現象が確認されている[11]。

アルツハイマー病 (Alzheimer's Disease: AD) は中高年発症の認知症を症状とする進行性疾患で，認知症の約半分を占める最も頻度の高い神経変性疾患である。AD 剖検脳においてアミロイドβの蓄積が多く報告され，これが AD の病態に関連していることが想定されている。家族性 AD 患者由来の iPS 細胞を神経細胞に分化誘導させるとアミロイドβが非 AD 患者由来の神経細胞に比べ 2～3 倍発現量が高いことが確認されている[12]。

(2) 創薬研究

iPS 細胞を用いて疾患病態のメカニズムを解明することで，新たな治療薬の開発が期待できる。先述の通り，SMA は疾患病態モデルの再現が行われ，それと同時に治療薬の開発も進められている。SMA は SMN1 および SMN2 遺伝子の変異が原因で SMN 蛋白産生量が減少するが，バルプロ酸およびトブラマイシンが SMN 蛋白を増加させることが報告されている。FD についても原因と考えられる IKBKAP スプライシング異常と神経分化異常を修復できる薬剤スクリーニングした結果，カイネチンが神経細胞への分化を促進したと報告されている。