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Parkin and Parkinson Disease

Hideki Shimura,[1,2,3*] Yoshikuni Mizuno,[1,4] and Nobutaka Hattori[1]

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.

[1] Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan; [2] Department of Neurology, Juntendo University Urayasu Hospital, Tokyo, Japan; [3] Institute for Environment and Gender-Specific Medicine, Juntendo University School of Medicine, Chiba, Japan; [4] Division of Neuroregenerative Medicine, Kitasato University School of Medicine, Sagamihara, Japan.
* Address correspondence to this author at: Department of Neurology, Juntendo University Urayasu Hospital, 2-1-1 Tomioka, Urayasu, Chiba 279-0021, Japan. Fax +81-47-304-8615; e-mail hshimura@juntendo-urayasu.jp.
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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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acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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