***Japan Academy Prize to:***

Nobutaka Hattori
Project Professor, Faculty of Medicine,
Juntendo University
Team Director, Neurodegenerative Disorders
Collaboration Laboratory, RIKEN Center for
Brain Science (CBS)
Director, Neuron-Glia Crosstalk Center Juntendo

for "Unraveling the Pathogenesis of Parkinson's Disease through Genetic Analysis"

***Outline of the work:***

Parkinson's disease (PD) is an intractable neurological disease and the second leading cause of neurodegenerative disorder after Alzheimer's disease. Recent advancements in symptomatic treatments have been remarkable, whereas nonmotor—such as dementia—and motor symptoms—including parkinsonism—considerably affect the quality of life. Thus, developing fundamental and disease-modifying treatments to decelerate disease progression remains a vital challenge. Since enrolling in graduate school, Dr. Nobutaka Hattori has been tackling this critical issue of determining the most important pathological mechanisms of PD. His notable achievements include the isolation and identification of the causative gene for young-onset PD, parkin, and the identification of its function. The parkin gene is the most frequently implicated causative gene for young-onset PD, and its isolation represents a groundbreaking discovery in neuroscience. Furthermore, Dr. Hattori and his team revealed that parkin functions as a ubiquitin ligase—a component of the protein degradation system. This finding determines the mechanisms of inclusion body formation observed in neurodegenerative diseases, such as PD, and provides new insights into neurodegeneration mechanisms.

Since this discovery, involving protein degradation system in the formation of inclusion bodies, predominantly observed in neurodegeneration, has been an essential phenomenon. Further, Dr. Hattori's team revealed that PINK1, a product of another causative gene for young-onset PD, collaborates with parkin to eliminate abnormal mitochondria through mitophagy, which is a type of autophagy–lysosome pathway. The finding indicating the interconnection between the ubiquitin–proteasome and autophagy–lysosome systems in neurological diseases is a notable breakthrough. In 2015, Dr. Hattori and his team isolated and identified CHCHD2—a mitochondrial-related gene—as a causative gene for hereditary PD. Furthermore, in 2020, they identified three familial cases of hereditary PD associated with the lysosome-related gene Prosaposin (Saposin D domain). To date, Dr. Hattori and his team solely isolated and identified three causative genes successfully for PD globally. Research on single-gene mutation-related PD is particularly effective in determining the

mechanisms of sporadic PD as functional analyses of these gene products reveal the underlying neurodegeneration mechanisms.

Recently, Dr. Hattori and his team have focused on developing novel biomarkers. They were the first to report that $\alpha$-synuclein ($\alpha$-Syn), which is the primary component of Lewy bodies and inclusions observed in PD and related disorders, propagates between cells and that $\alpha$-Syn seeds are present in the blood. Synucleinopathies—a group of diseases characterized by $\alpha$-Syn aggregation observed in neuropathology—include PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Early in the disease course, differentiating these three disorders solely based on clinical symptoms is challenging. However, Dr. Hattori and his team discovered that the structure of circulating $\alpha$-Syn seeds in the blood varies among these diseases, enabling early differential diagnosis. This technology has garnered global attention as it may enable diagnosis even at the prodromal stage before the onset of parkinsonism. Beyond $\alpha$-Syn, Dr. Hattori and his team have been investigating other PD biomarkers, identifying clinically applicable markers, such as caffeine, polyamines, and RNA, derived from sebaceous glands, which have received high acclaim.

Over the past 30 years, Dr. Hattori has been actively conducting genetic mutation screenings and functional analyses of gene products for hereditary PD, achieving several groundbreaking results. He is globally regarded as a leading authority in PD genetics research. In 2018, he organized a symposium in Japan titled “The 20th Anniversary of Parkin Discovery—To the Past, the Present, and the Future” at the 41st Annual Meeting of the Japan Neuroscience Society, supported by Elsevier. In 2015–2017, he served as the Asia and Oceania Section Chair of the International Congress of Parkinson’s Disease and Movement Disorders® (MDS), which is the largest international organization for movement disorder-related diseases. During his tenure, he contributed to educating physicians and healthcare professionals in the region and raising awareness among patients. He was awarded the C. David Marsden Lecture Award by MDS in 2022 for his outstanding contributions to basic research and elected an Honorary Member of the society in 2023.

Dr. Hattori is a globally recognized leader in PD research and an active clinician who continues to care for several patients. He is a compassionate physician who pays meticulous attention to the needs of patients with PD and their families. His relentless pursuit of scientific discovery as an exceptional researcher, in addition to dedication to uncovering new diagnostic and therapeutic approaches through patient interactions as a clinician, makes him an outstanding medical scientist. Therefore, Dr. Nobutaka Hattori’s achievements are deemed genuinely worthy of the Japan Academy Prize.

**List of Main Publications** (* Corresponding author)

1. Kitada, T, Asakawa, S, Hattori, N, Matsumine, H, Yamamura, Y, Minoshima, S, Yokochi, M, Mizuno, Y, and Shimizu, N*: Mutations in the parkin gene cause

autosomal recessive juvenile parkinsonism, **Nature**, 392; 605–608, 1998.

2. Hattori, N*, Kitada, T, Matsumine, H, Asakawa, S, Yamamura, Y, Yoshino, H, Kobayashi, T, Yokochi, M, Wang, M, Yoritaka, A, Kondo, T, Kuzuhara, S, Nakamura, S, Shimizu, N, and Mizuno, Y*: Molecular genetic analysis of a novel Parkin gene in Japanese families with autosomal recessive juvenile parkinsonism: Evidence for variable homozygous deletions in the Parkin gene in affected individuals. **Ann. Neurol.**, 44; 935–941, 1998.
3. Shimura, H, Hattori, N, Kubo, S, Mizuno, Y, Asakawa, S, Minoshima, S, Shimizu, N, Iwai, K, Chiba, T, Tanaka, K*, and Suzuki. T: Familial Parkinson disease gene product parkin is a ubiquitin-protein ligase. **Nat. Genet.**, 25; 302–305, 2000.
4. Hattori, N*, and Mizuno, Y: Pathogenetic mechanisms of parkin in Parkinson's disease. Review, **Lancet**, 364; 722–724, 2004.
5. Matsuda, N, Sato, S, Shiba, K, Okatsu, K, Saisho, K, Gautier, CA, Sou, Y-S, Saiki, S, Kawajiri, S, Sato, F, Kimura, M, Komatsu, M, Hattori, N, and Tanaka, K*: PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. **J. Cell Biol.**, 189; 211–221, 2010.
6. Okatsu, K, Oka, T, Iguchi, M, Imamura, K, Kosako, H, Tani, N, Kimura, M, Go, E, Koyano, F, Funayama, M, Shiba-Fukushima, K, Sato, S, Shimizu, H, Fukunaga, Y, Taniguchi, H, Komatsu, M, Hattori, N, Mihara, K, Tanaka, K, and Matsuda, N*: PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria, **Nat. Commun.**, 3; 1016, 2012.
7. Nishioka, K, Hayashi, S, Farrer, MJ, Singleton, AB, Yoshino, H, Imai, H, Kitami, T, Sato, K, Kuroda, R, Tomiyama, H, Mizoguchi, K, Murata, M, Toda, T, Imoto, I, Inazawa J, Mizuno, Y, and Hattori, N*: Clinical heterogeneity of $\alpha$-synuclein gene duplication in Parkinson's disease. **Ann. Neurol.**, 59; 298–309, 2006.
8. Shimura, H, Schlossmacher, MG, Hattori, N, Frosch, MP, Trockenbacher, A, Schneider, R, Mizuno, Y, Kosik, KS, and Selkoe, DJ*: Ubiquitination of a new form of alpha-synuclein by parkin from human brain: Implications for Parkinson's disease. **Science**, 293; 263–269, 2001.
9. Funayama, M, Ohe, K, Amo, T, Furuya, N, Yamaguchi, J, Saiki, S, Li, Y, Ogaki, K, Ando, M, Yoshino, H, Tomiyama, H, Nishioka, K, Hasegawa, K, Saiki, H, Satake, W, Mogushi, K, Sasaki, R, Kokubo, Y, Kuzuhara, S, Toda, T, Mizuno, Y, Uchiyama, Y, Ohno, K, and Hattori, N*: CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. **Lancet Neurol.**, 14; 274–282, 2015.
10. Meng, H, Yamashita, C, Shiba-Fukushima, K, Inoshita, T, Funayama, M, Sato, S, Hatta, T, Natsume, T, Umitsu, M, Takagi, J, Imai, Y*, and Hattori, N*: Loss of Parkinson's disease-associated protein CHCHD2 affects mitochondrial crista structure and destabilizes cytochrome c. **Nat. Commun.**, 8; 15500, 2017.
11. Oji, Y, Hatano, T, Ueno, SI, Funayama, M, Ishikawa, KI, Okuzumi, A, Noda, S, Sato, S,

Satake, W, Toda, T, Li, Y, Hino-Takai, T, Kakuta, S, Tsunemi, T, Yoshino, H, Nishioka, K, Hattori, T, Mizutani, Y, Mutoh, T, Yokochi, F, Ichinose, Y, Koh, K, Shindo, K, Takiyama, Y, Hamaguchi, T, Yamada, M, Farrer, MJ, Uchiyama, Y, Akamatsu, W, Wu, YR, Matsuda, J, and Hattori, N*: Variants in saposin D domain of prosaposin gene linked to Parkinson's disease. **Brain**, 143; 1190–1205, 2020.

12. Mori, A, Hatano, T, Inoshita, T, Shiba-Fukushima, K, Koinuma, T, Meng, H, Kubo, SI, Spratt, S, Cui, C, Yamashita, C, Miki, Y, Yamamoto, K, Hirabayashi, T, Murakami, M, Takahashi, Y, Shindou, H, Nonaka, T, Hasegawa, M, Okuzumi, A, Imai, Y, and Hattori, N*: Parkinson's disease- associated iPLA2-VIA/PLA2G6 regulates neuronal functions and α-synuclein stability through membrane remodeling. **Proc. Natl. Acad. Sci. U.S.A.**, 116; 20689–20699, 2019.
13. Hattori, N, Tanaka, M, Ozawa, T, and Mizuno, Y*: Immunohistochemical studies on Complex-I Complex-II Complex-III and Complex-IV of mitochondria in Parkinson's disease. **Ann. Neurol.**, 30; 563–571, 1991.
14. Yoritaka, A, Hattori, N*, Uchida, K, Tanaka, M, Stadtman, ER, and Mizuno, Y: Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease, **Proc. Natl. Acad. Sci. U.S.A.**, 93; 2696–2701, 1996.
15. Shimura-Miura, H, Hattori, N*, Kang, D, Miyako, K, Nakabeppu, Y, and Mizuno, Y: Increased 8-oxo-dGTPase in the mitochondria of substantia nigral neurons in Parkinson's disease. **Ann. Neurol.**, 46; 920–924, 1999.
16. Satake, W, Nakabayashi, Y, Mizuta, I, Hirota, Y, Ito, C, Kubo, M, Kawaguchi, T, Tsunoda, T, Watanabe, M, Takeda, A, Tomiyama, H, Nakashima, K, Hasegawa, K, Obata, F, Yoshikawa, T, Kawakami, H, Sakoda, S, Yamamoto, M, Hattori, N, Murata, M, Nakamura, Y, and Toda, T*: Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. **Nat. Genet.**, 41; 1303–1307, 2009.
17. Hatano, T, Saiki, S, Hattori, N, Okuzumi, A, Mohney, RP, and Hattori, N*: Identification of novel biomarkers for Parkinson's disease by metabolomic technologies. **J. Neurol. Neurosurg. Psychiatry**, 87; 295–301, 2016.
18. Fujimaki, M, Saiki, S*, Li, Y, Kaga, N, Taka, H, Hatano, T, Ishikawa, KI, Oji, Y, Mori, A, Okuzumi, A, Koinuma, T, Ueno, SI, Imamichi, Y, Ueno, T, Miura, Y, Funayama, M, and Hattori, N*: Serum caffeine and metabolites are reliable biomarkers of early Parkinson disease. **Neurology**, 90; e404–e411, 2018.
19. Okuzumi, A, Kurosawa, M, Hatano, T, Takanashi, M, Nojiri, S, Fukuhara, T, Yamanaka, T, Miyazaki, H, Yoshinaga, S, Furukawa, Y, Shimogori, T, Hattori, N*, and Nukina, N*: Rapid dissemination of alpha-synuclein seeds through neural circuits in an in-vivo prion-like seeding experiment. **Acta Neuropathol. Commun.**, 6; 96, 2018.
20. Saiki, S*, Sasazawa, Y, Fujimaki, M, Kamagata, K, Kaga, N, Taka, H, Li Y, Souma, S, Hatano, T, Imamichi, Y, Furuya. N, Mori A, Oji Y, Ueno SI, Nojiri S, Miura Y, Ueno T, Funayama, M, Aoki, S, and Hattori, N*: A metabolic profile of polyamines in parkinson

disease: A promising biomarker. **Ann. Neurol.**, 86; 251–263, 2019.

21. Sasazawa, Y, Souma, S, Furuya, N, Miura, Y, Kazuno, S, Kakuta, S, Suzuki, A, Hashimoto, R, Hirawake-Mogi, H, Date, Y, Imoto, M, Ueno, T, Kataura, T, Korolchuk, VI, Tsunemi, T, Hattori, N*, and Saiki, S*: Oxidative stress-induced phosphorylation of JIP4 regulates lysosomal positioning in coordination with TRPML1 and ALG2. **EMBO J.**, 41; e111476, 2022.
22. Hattori N*: Elsevier/NSR Symposium: The 20th Anniversary of Parkin Discovery—To the Past, the Present, and the Future. **Neurosci. Res.**, 159; 1–2, 2020.
23. Uehara, Y, Ueno, SI, Amano-Takeshige, H, Suzuki S, Imamichi, Y, Fujimaki, M, Ota, N, Murase, T, Inoue, T, Saiki, S*, and Hattori, N*: Non-invasive diagnostic tool for Parkinson's disease by sebum RNA profile with machine learning. **Sci. Rep.**, 11; 18550, 2021.
24. Miyamoto, K, Saiki, S*, Matsumoto, H, Suzuki, A, Yamashita, Y, Iseki, T, Ueno, SI, Shiina, K, Kataura, T, Kamagata, K, Imamichi, Y, Sasazawa, Y, Fujimaki, M, Akamatsu, W, and Hattori, N*: Systemic Metabolic Alteration Dependent on the Thyroid-Liver Axis in Early PD. **Ann. Neurol.**, 93; 303–316, 2023.
25. Okuzumi, A, Hatano, T, Matsumoto, G, Nojiri, S, Ueno, S-I, Imamichi-Tatano, Y, Kimura, H, Kakuta, S, Kondo, A, Fukuhara, T, Li, Y, Funayama, M, Saiki, S, Taniguchi, D, Tsunemi, T, McIntyre, D, Gérardy, J-J, Mittelbronn, M, Kruger, R, Uchiyama, Y, Nukina, N, and Hattori, N*: Propagative $\alpha$-synuclein seeds as serum biomarkers for synucleinopathies. **Nat. Med.**, 29; 1448–1455, 2023.