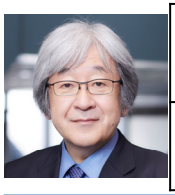
【Grant-in-Aid for Scientific Research (S)】

Elucidation of mechanism of propagation and aggregation of alpha-synuclein and development of disease-modifying therapies



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Project Information	Project Number : 24H00068　Project Period (FY) : 2024-2028 Keywords : Parkinson's disease, α-synuclein, Levy bodies, IP/RT-QuIC, protein propagation

Purpose and Background of the Research

●Outline of the Research

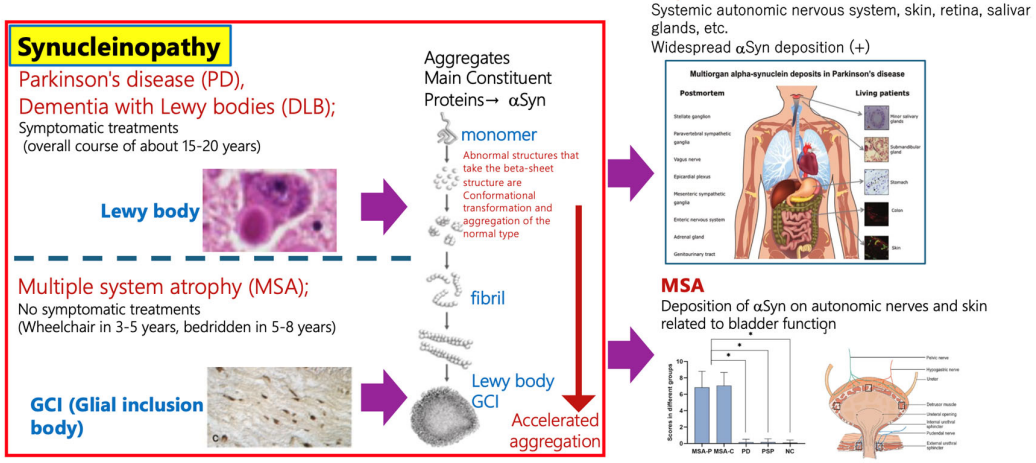
Parkinson's Disease (PD) is a progressive neurodegenerative disorder with no current cure or treatment to slow its progression. As Japan's population ages, PD is becoming increasingly prevalent, making the development of disease-modifying therapies crucial. Early diagnosis and treatment are key, requiring a better understanding of the formation of Lewy bodies and the propagation of its main protein, α-synuclein (αSyn).

This research aims to:

1) Using the technology of Immunoprecipitation-based real-time quaking-induced conversion (IP/RT-QuIC), which we were the first in the world to prove its existence, we will clarify the propagation and aggregation mechanism of αSyn, the main constituent protein of Lewy bodies.

2) By analyzing the function of the product of the responsible gene for hereditary PD focusing on the propagation and aggregation mechanism of αSyn, we will elucidate the disease onset mechanisms. In synucleinopathies, as shown in the figure below, there are Parkinson's disease, Lewy body dementia, and multiple system atrophy with poor prognosis. Neuropathologically, there are Lewy bodies and glial inclusions, both of which are mainly composed of α-synuclein. Interestingly, it has been reported that it is deposited not only in the brain but also in several organs. It is also deposited in the skin and cannot be explained by nerve-to-nerve transmission alone. It is pointed out that abnormal αSyn seeds are likely to propagate not only through nerve-to-nerve transmission but also through the blood. In this project, we will clarify why Lewy bodies and glial inclusions are formed, focusing on the propagation of abnormal α-synuclein. In addition, we will elucidate the onset mechanism from the pathology of hereditary PD.

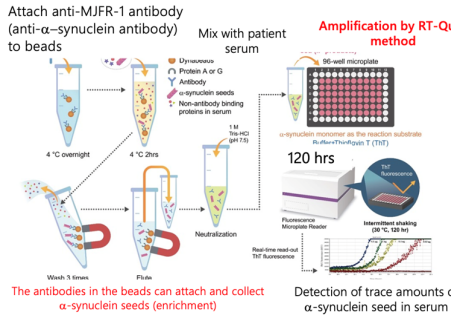
Elucidation of α-synuclein aggregation mechanism and its propagation mode⇒Leading to the investigation of the essential cause of the disease



α-Synuclein proteins are deposited not only in the brain but also throughout the body. ⇒ The mode of transmission is unknown.

●How did I come up with the idea for this research?

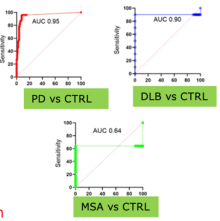
We postulated the existence of abnormal α-synuclein seeds in the blood due to their body-wide distribution, including the skin. Their presence in cerebrospinal fluid was established, but we expected low levels in blood. Through immunoprecipitation, we verified their presence in blood (Nat Med 2023). We observed that the structure of these seeds changes with synucleinopathies, suggesting clinical types might be seed structure-dependent. We also detected that 24-34% of individuals with REM sleep behavior disorder, a synucleinopathy risk group, tested positive. This implies potential early identification of high-risk groups before parkinsonism onset. If early diagnosis is achievable, we propose a treatment to eliminate these seeds from the blood as a potential disease-modifying therapy. This led to our research proposal.



Establishment of biomarkers with high diagnostic potential

Diagnosis	IP/RT-QuIC Results +/Total	Positive Results
Alpha-synucleinopathies		
PD	210/211	95%
MSA	25/39	64%
DLB	9/10	90%
Non- Alpha-synucleinopathies		
PSP	1/ 30	3%
AD	4/ 25	16%
Controls	11/ 128	8.5%
Park2 mutation patients	0/ 17	0%

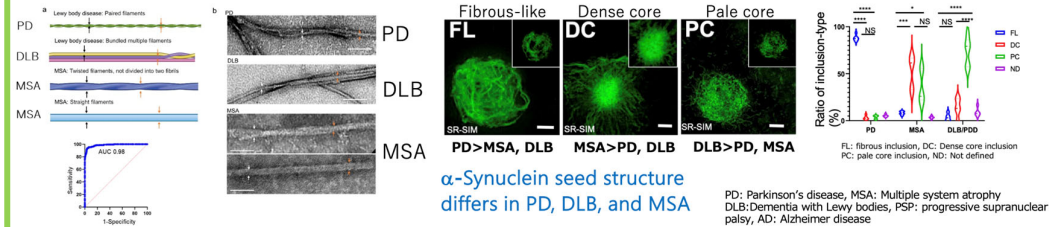
PD: 221cases
Healthy controls: 128cases
Sensitivity 96.7
Distinguishable with specificity 86.2



Expected Research Achievements

We aim to achieve the following tasks [1)-6)] during the research period: 1) Develop a more user-friendly blood diagnostic system using IP/RT-QuIC, 2) Conduct diagnostic research on REM Sleep Behavior Disorder (RBD) and hereditary PD risk groups using IP/RT-QuIC, 3) Analyze the distribution of abnormal αSyn seeds across organs and brain regions using IP/RT-QuIC, 4) Study the mechanism of Lewy body formation and αSyn aggregate breakdown, 5) Investigate the onset mechanism of sporadic PD based on the pathomechanisms of hereditary PD related to αSyn propagation control, 6) Establish a disease-modifying therapy (plasma exchange therapy) for synucleinopathies. We've found that seed structure varies by synucleinopathy (see figure below) and aim to develop a technology for early differentiation based on these differences. We'll use the RT-QuIC method to verify early diagnostic technology and organ-to-organ transmission. We've confirmed that RT-QuIC can be applied to paraffin sections.

Establishment of a differential method for synucleinopathies



α-Synuclein seed structure differs in PD, DLB, and MSA

PD: Parkinson's disease, MSA: Multiple system atrophy
DLB:Dementia with Lewy bodies, PSP: progressive supranuclear palsy, AD: Alzheimer disease

●Establishment of disease-modifying therapy to halt the progression of synucleinopathies

We aim to develop new treatments in tasks 4), 5), and 6). We aim to establish a therapy to prevent the propagation and removal of abnormal αSyn seeds (plasma exchange therapy).

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