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# Relationship Between ATP Production and Genotypes in Parkinsonism with Indication of their Deletion

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**Abstract**

The second most common age-related neurodegenerative condition affecting the central nervous system is Parkinson's disease. Lewy bodies and significant dopaminergic neuron degeneration in the substantia nigra pars compacta are hallmarks of Parkinson's Disease (PD) neuropathology. This results in a severe striatal dopamine deficiency, which impairs motor functions. Among the clinical motor characteristics of Parkinson's Disease (PD) are bradykinesia, resting tremors, slowness of movement, muscle rigidity, and postural instability.

Dulbecco's modified Eagle's medium supplemented with 10% (v/v) fetal calf serum and 5% (v/v) Pen Strep Penicillin-Streptomycin (50 pg/ml) was used to cultivate mouse embryonic fibroblasts from wild-type, CHOP-knockout, and HtrA2 KO mice. The cells were then kept in a humidified incubator at 37°C with 5% $CO_2$.

Treatment with 6-OHDA in combination with ADEP4 or ACP5 has demonstrated that these medications may have a protective impact on CHOP-KO ATP generation. A combined HtrA2-KO/CHOP-KO model was used to examine combinations of positive and negative transcriptional feedback regulation.

Transcriptional mitochondrial quality control is eliminated when mitochondrial stress signaling is compromised. ADEP4 and ACP5, which have been demonstrated to induce mitochondrial stress signaling, were administered to mouse embryonic fibroblasts derived from wild-type, CHOP-knockout, and HtrA2-KO mice in order to ascertain the role of HtrA2 and CHOP in the transcriptional activation of the mitochondrial stress response. The current study concludes that in Parkinson's disease, HtrA2 and CHOP contribute to the transmission of stress signaling and the subsequent activation of mitochondrial quality control.

**Keywords:** ADEP4, ACP5, parkinson's disease, 6-OHDA, HtrA2 KO, mitochondrial quality control

**Article History**

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## INTRODUCTION

Parkinson's Disease (PD) is the second most prevalent age-related neurodegenerative disorder of the central nervous system (CNS), affecting over 2% of the worldwide population older than 65 years.[1,2] The neuropathology of PD is characterized by the presence of Lewy bodies and prominent degeneration of dopaminergic neurons in the Substantia Nigra Pars Compacta (SNpc), which leads to severe striatal dopamine (DA) deficit, resulting in motor impairment. Bradykinesia, resting tremors, slowness of movement, muscular rigidity and postural instability comprise some of the clinical motor features of PD (Fig. 1).

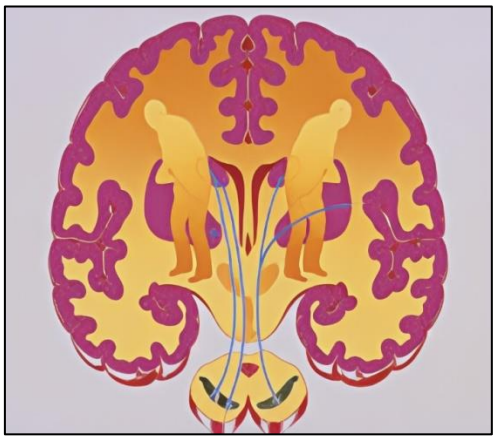

**Figure 1.** Parkinson's Disease (PD) Neuropathology is Characterized by Substantia Nigra Pars Compacta.

Patients may also develop non-clinical manifestations such as autonomic impairment, cognitive variations, depression, sleep disturbances and in the late stages dementia.[2,3] Parkinson's disease is a heterogeneous, multifactorial and often complex neurodegenerative disease. Although the specific pathogenesis involving PD remains under investigation, several pathological studies propose that environmental factors and genetic background as well as their interaction might influence the risk of developing this age-related neurodegenerative disorder.[4,5]

Additionally, numerous molecular mechanisms have been related to operate in conjunction to promote dopaminergic neuro-degeneration, such as Reactive Oxygen Species (ROS) production through increased cellular stress, dysfunction of mitochondria, abnormal protein aggregation and misfolding due to oxidative and Endoplasmic Reticulum (ER) stress, abnormal cytoplasmic protein inclusions, neuro-inflammation and autophagic impairment.[6,7]

### Parkinson's Disease History

The symptoms of Parkinson's disease were described by James Parkinson (1755-1824) as a “shaking palsy”. He was an English surgeon, geologist, neurologist and political activist. Disease has been recognized from ancient times as a ‘shaking palsy’ (India and Europe AD175).

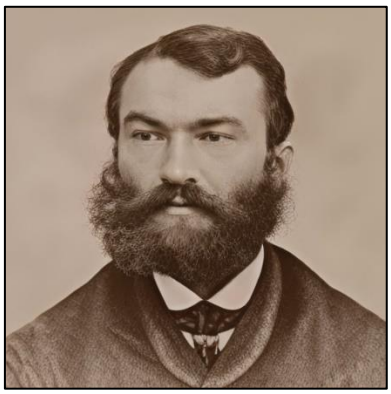

**Figure 2.** James Parkinson (1755–1824) defined Parkinson's Disease Symptoms as "shaking palsy." He was a political activist, neurologist, geologist, and surgeon from England.

In 1817, Dr. James Parkinson published 'An Essay on the Shaking Palsy' which contained 6 cases of PD. 60 years later, Jean Marie Charcot, French neurologist, recognized the importance of the study and named the disease after him (Fig. 2).

In 1960s, chemical differences in the brains of PD patients were identified. Levodopa was first administered and is still gold standard medication which led Arvid Carlsson, Oleh Hornykiewicz, George Cotzias, and Melvin Yahr to win Nobel Prize in 2000 for their studies initiated with "reserpine induced Parkinsonism in animal models". Last about 20 years genetic studies have contributed to understanding the disease etiopathogenesis.

**Parkinson's Disease Incidence**

The incidence of this disease is 0.2% in western societies (about 127000 in UK). About 90% of those cases are found in patients older than 50 years old. According to genders, we found that 30.9/10000 (95% Confidence intervals is ranged between 30.1 and 31.8) for males and 24.1/10000 (95% confidence intervals is ranged between 23.3 and 24.8) for females. The rates throughout the world are similar (Fig. 3).

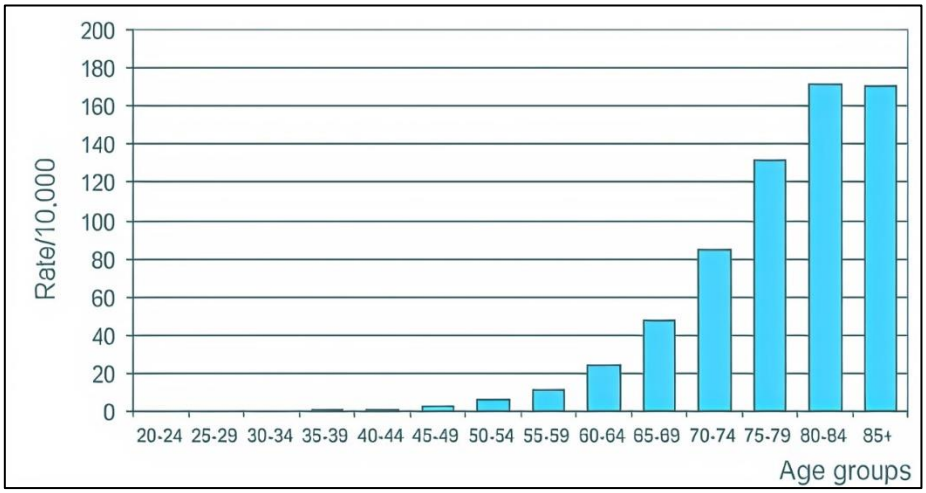


**Figure 3.** Prevalence of Parkinson's Disease Among Age Groups for Rate/10000.

**Lewy Bodies and Lewy Neuritis**

Lewy bodies are abnormal aggregates of protein that develop inside nerve cells in Parkinson's disease (PD), Lewy body dementia, and some other disorders. They are identified under the microscope when histology is performed on the brain.

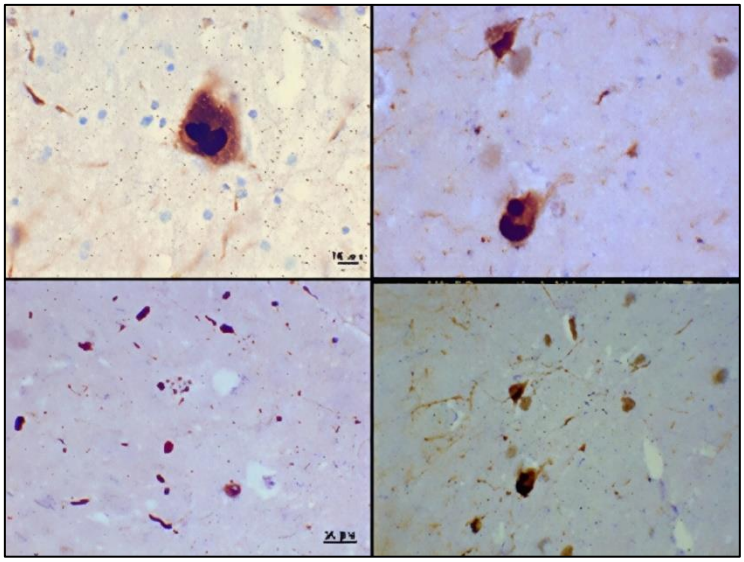

**Figure 4.** In Parkinson's Disease (PD), Lewy Body Dementia, and some other Conditions, Aberrant Protein Aggregates called Lewy Bodies form Inside Nerve Cells. When Histology is done on the Brain, they are Recognized Under a Microscope.

 

Patients afflicted with this disease are characterized by appearance of abnormal bodies (protein aggregates) developing inside nerve cells seen in brain tissue from patients with Parkinson's disease (Fig. 4).

**Break Staging System in Parkinson's Disease**

Initiation sites in the brain of the patients are divided into 6 break stages. In break stage 1 and 2, disturbance occurs in autonomic and olfactory nerves. Break stage 3 and 4 are characterized by sleep and motor disturbances and in break stage 5 and 6 emotional and cognitive disturbances take the place as shown in the figure 5 below.

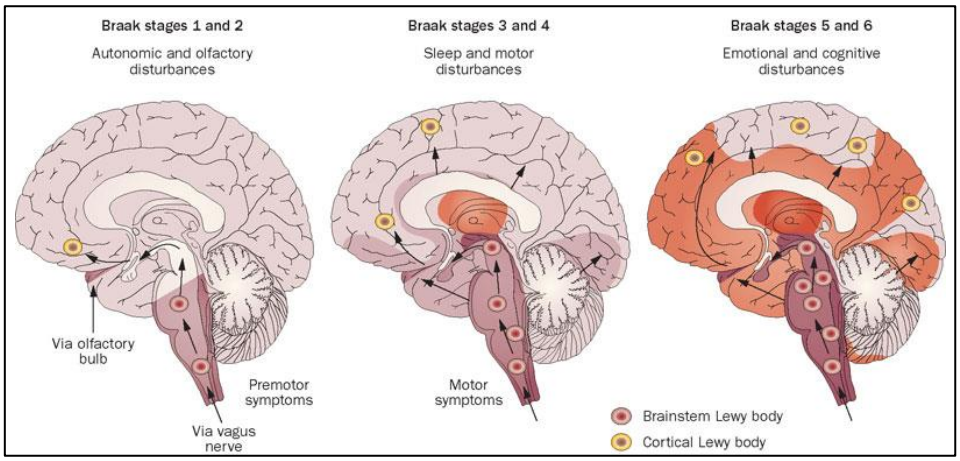


**Figure 5.** Initiation Sites in the Olfactory Bulb and the Medulla Oblongata, through to the later Infiltration of Lewy Pathology into Cortical Regions.

**Parkinson's Disease Pathophysiology**

Basal ganglia controls movement. Dopamine is considered as an inhibitory neurotransmitter in the basal ganglia while acetylcholine is an excitatory neurotransmitter in the basal ganglia. Without dopamine, inhibitory influences are lost and excitatory mechanisms are unopposed which leads to overstimulation of neurons in the basal ganglia and hence excess muscle tone occurs with tremors and rigidity (Fig. 6).

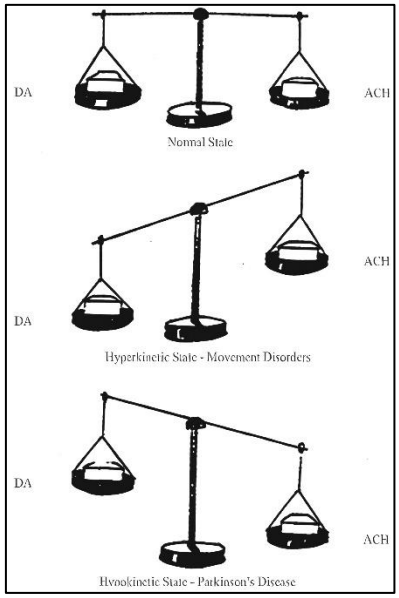


**Figure 6.** Balance between Dopamine and Acetylcholine in the Basal Ganglia leads to Normal State. Excess Dopamine Leads to Hyperkinetic State Characterized by Movement Disorders. Excess Acetylcholine Leads to Hypokinetic State Which is the Key Symptom of Parkinson's Disease.

**Parkinson's Disease Clinical Presentation**

Clinical presentation motor symptoms are hypokinesia which is defined as lack of initiation of movement caused by excess acetylcholine, bradykinesia or slow movement, muscle rigidity or cog-wheel rigidity, joint stiffness, resting tremors, shuffling gait, expressionless face or mask face, micrographia and dementia in more severe cases.

The classical syndrome triad composed of tremors, rigidity and bradykinesia. These maybe absent initially, when non-specific symptoms of tiredness, aching limbs, mental slowness, depression and small handwriting (micrographia) maybe noticed. Although Parkinsonian features are initially unilateral, gradual bilateral involvement is the rule. A resting tremor in an upper limb is being a common presenting feature. Cogwheel rigidity occurs mostly in the upper limbs with superimposed tremor, felt as tightness or stiffness of muscles, ratchet-like (catch-release-catch-release like movement). The plastic or lead pipe type mostly occurs in the legs and characterized by stiffness (in the neck, trunk and shoulders) and posture (as head bowed, body bent forward, arms flexed, thumbs turned into palms and knees bent slightly).

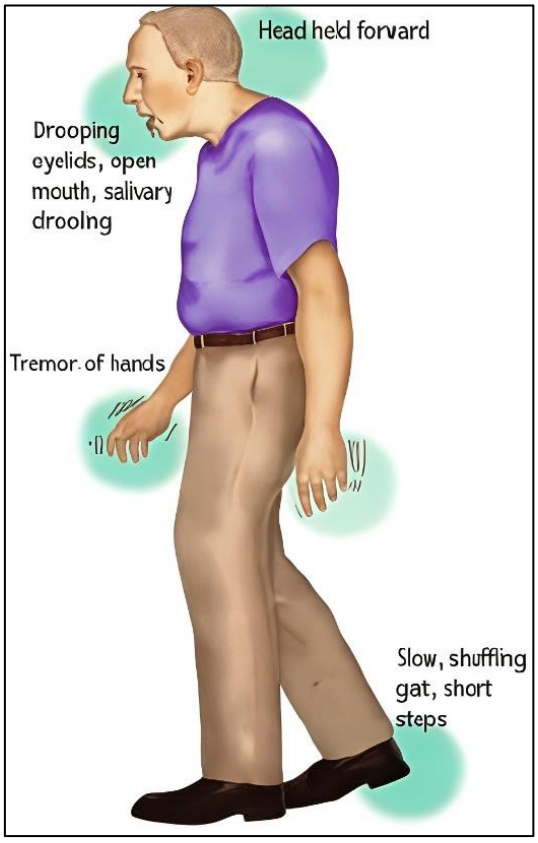


**Figure 7.** Parkinson's Disease Clinical Motor Presentation.

It is characterized by head held forward, dropping eyelids, open mouth, salivary drooling, hands' tremors and movement slowness, shuffling gait and short steps (Fig. 7).

Bradykinesia may develop gradually. It is defined as slowed ability to start and continue movements, and impaired ability to adjust the body's position. It can be developed into slow movement or even akinesia which is loss of movement and poker face which is expressionless face (masked face), dysphonia which is slow speech-softer and indistinct and dysphagia or drooling. In general, slowness in initiating or repeating movements, as slowness of gait and difficulty with tasks as fastening buttons, shaving or writing (micrographia).

According to abnormal gait or posture it is asymmetrical because it is characterized by slow to start walking, shortened stride, stiff legged gait-rigidity comes through one side, therefore difficult clearing swinging on one side, festination which is rapid, small steps and tendency to run, reduced arm swing usually unilateral, impaired balance on turning and leads with head and shoulders. Also fall forward down is known by turned posture-postural righting reflexes are impaired early, but falls tend not to occur until later.

There are a number of abnormalities on neurological examination like muscle strength and

 

reflexes remain normal, plantar responses are flexor. There is a paucity of facial expression (hypomimia) and the blink reflex may be exaggerated and fail to habituate (glabellar tap sign).

Eye movements are normal to standard clinical testing, provided allowance is made for the normal limitation of upward gaze with age. Sensation is normal and intellectual abilities are not affected initially. As the disease progresses, 1/3 develop cognitive impairment. Parkinson's disease commonly associated with other features; loss of smell, depression, dementia, autonomic dysfunction, sleep disturbance due to involvement of other non-dopaminergic structures as disease progresses.

**Drug Induced Parkinsonism**

It is important because it is reversible although it may require weeks or months to reverse after drug discontinuation e.g. Dopamine antagonists; neuroleptic agents (Haloperidol), atypical neuroleptic agents, Calcium Channel Blockers (flunarizine, cinnarizine), Amiodarone, valproic acid and lithium (by uncertain mechanisms). Dopamine antagonists also exacerbate Parkinson's disease and should be avoided if possible in the treatment of patients with the disease.

**Parkinson's Disease and Dopamine**

L-3, 4-dihydroxyphenylalanine (L-DOPA) is a precursor of dopamine. Although the number of dopamine-releasing terminals in striatum is diminished in Parkinson's disease, remaining neurons can be driven to produce more dopamine by administering its precursor, L-DOPA. D-DOPA is not active as a pro-drug (Fig. 8).


**Figure 8.** Chemical structure of L-3, 4-dihydroxyphenylalanine (L-DOPA) with the Most Famous Products.

**Anticholinergic Therapy**

Muscarinic receptor antagonists (anticholinergic drugs) have a useful effect on tremor and rigidity, but do not help bradykinesia. They can be prescribed early in the disease before bradykinesia is a problem, but should be avoided in elderly patients in whom they cause confusion, dementia or hallucination.

Other side effects include dry mouth, blurred vision, difficulty with micturition and constipation. Many anticholinergics are available as trihexyphenidyl (benzhexol; 1-4 mg every 8 hours) and orphenadrine (50-100 mg every 8 hours) (Fig. 9).

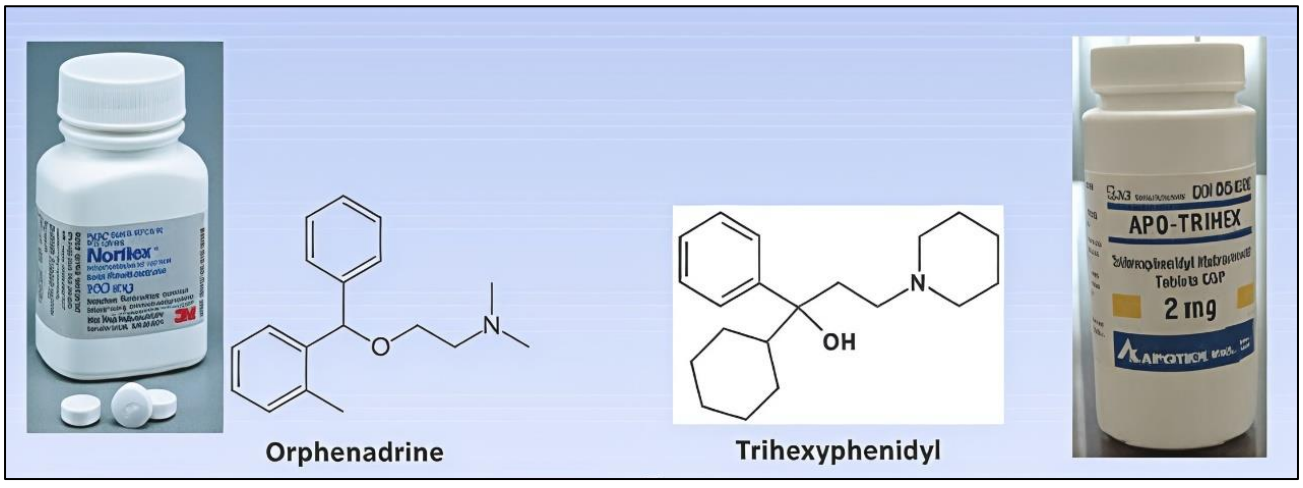


**Figure 9.** Anticholinergic Drugs which can be used for PD with their Chemical Structures Orphenadrine (Norflex) and Trihexyphenidyl (Apo-Trihex).

Now aim to prolong the pharmacological dopaminergic stimulation of the striatum to limit the development of motor fluctuations. In younger patients, preference is given to neuroprotective and L-DOPA sparing therapies. L-DOPA should only be started to help overcome significant disability.

In young patients whose age is less than 65 years old, we aim to avoid L-DOPA for as long as possible, although all patients eventually need it, and tend to use long-acting dopamine agonist with half-life more than 8 hours as initial dose. L-DOPA can be given concomitantly with peripheral COMT inhibitors such as entacapone, $MAO_B$ inhibitors e.g. selegiline which may retard the progression of diseases or $D_1$ and $D_2$ receptor agonists (Fig 10).

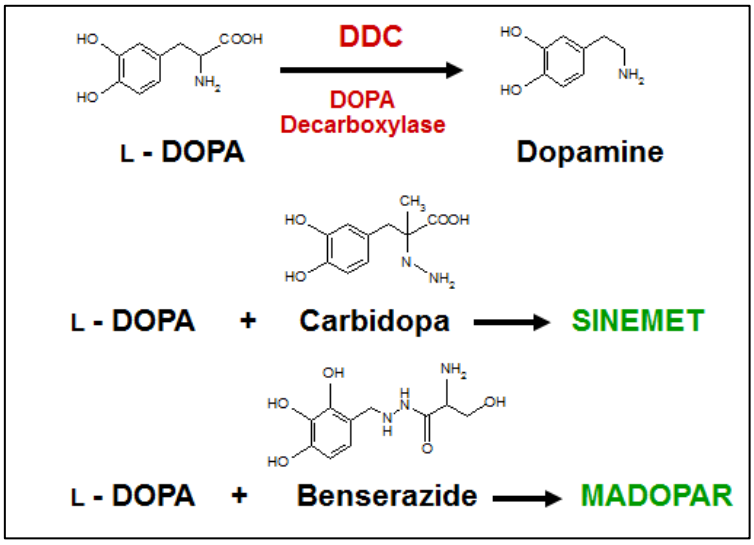


**Figure 10.** Use of peripheral inhibitors of DOPA Decarboxylase (DDC) in PD.

## MATERIALS AND METHODS

### Parkinson's Disease Diagnosis

There is no standard diagnostic test. The main causes of this disease are toxins especially manganese and carbon monoxide poisoning which can cause structural CNS lesions, metabolic disorders and other neurologic disorders. Most are rare and suggested by atypical features, history or exam. Routinely it is needed to consider 2 alternative diagnoses:

- Drug induced parkinsonism.
- Parkinsonism plus syndromes: parkinsonian features with other neurological signs atypical for PD.

Imaging is the ultimate test to detect dopaminergic loss but only available in specialized units and very expensive (Fig. 11,12).

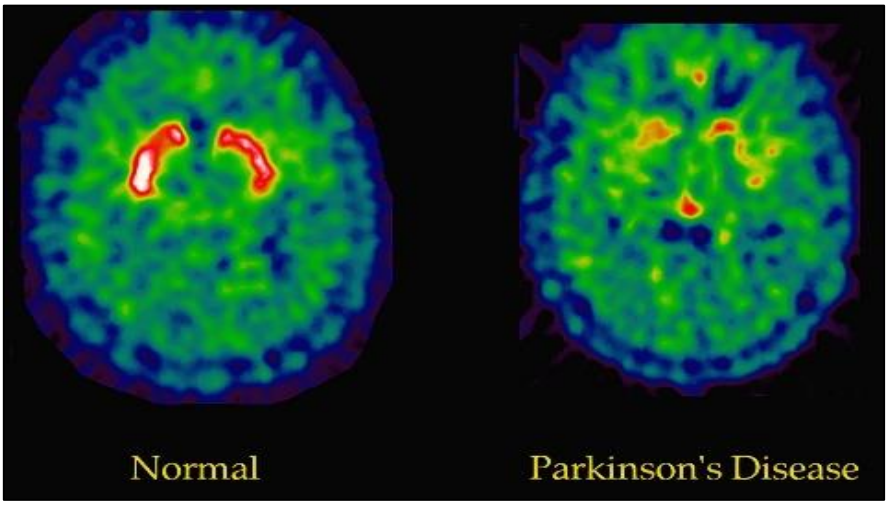


**Figure 11.** PET Scan Showing Localization of $^{18}$F-fluoro DOPA Incorporation in the Brains of a Normal Subject and a Patient with Parkinson's Disease.

 

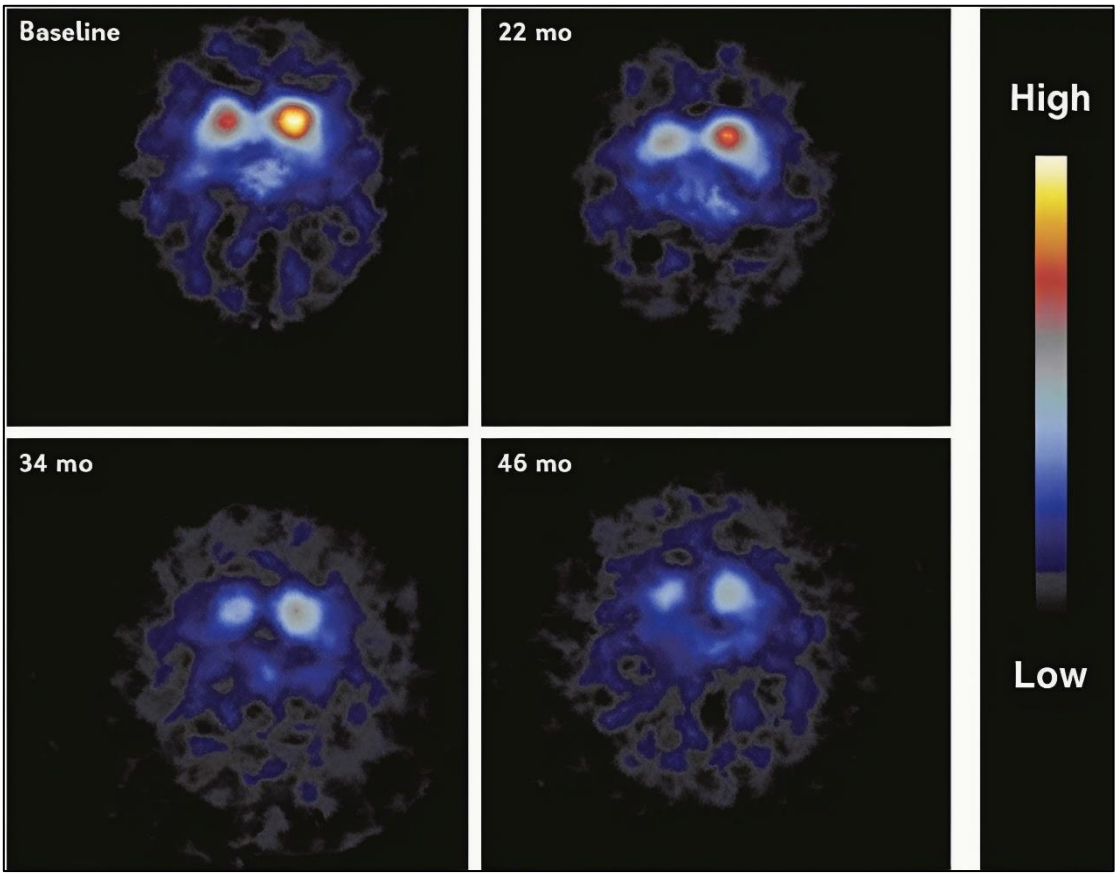


**Figure 12.** PET Scans Showing Progressive Loss of Dopamine during Parkinson's Disease.

**Cell Culture**

Mice embryonic fibroblasts (MEFs) obtained from wild-type (WT), CHOP-knockout (KO) and HtrA2 KO were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) fetal calf serum (FCS) and 5% (v/v) Pen Strep Penicillin-Streptomycin (50 pg/ml) and stored in a humidified incubator at 37°C in the presence of 5% $CO_2$. Cells were passaged every 3-4 days with 0.1% trypsin. Cell viability and cell numbers were determined using a haemocytometer.

**ATP Production is Decreased in HtrA2 KO/CHOP Genotype**

Drug treatment with 6-OHDA in conjunction with ADEP4 or ACP5 have illustrated that these drugs might have a protective effect in ATP production of CHOP-KO. When compared to the genotypes treated only with 6-OHDA, energy production was significantly less decreased in HtrA2/CHOP KO genotype treated in conjunction with ADEP4 or ACP5. ATP production was significantly higher in HtrA2/CHOP KO genotype ($p < 0.0001$), suggesting that CHOP might be important to HtrA2 transcription activation.

**Deletion of both HtrA2 and CHOP Indicates a Plausible Transcriptional Feedback Loop**

Combinations of positive and negative transcriptional feedback regulation were analyzed by introducing a combined HtrA2 KO/CHOP KO model. In response to removal of both HtrA2 and CHOP in cells, the results have indicated that this suppression might create a complex feedback loop mechanism that CHOP is required for transcriptional activation of mitochondrial quality control both at molecular level (mtUPR) and organellar level (mitophagy).

**RESULTS**

Impaired signaling of mitochondrial stress abolishes transcriptional mitochondrial quality control. To determine the involvement of HtrA2 and CHOP in the transcriptional activation of the mitochondrial stress response, mice embryonic fibroblasts (MEFs) obtained from wild-type (WT), CHOP knockout (KO) and HtrA2 KO were treated with ADEP4 and ACP5, drugs which have been showed to induce mitochondrial stress signaling. These genotypes were chosen based on previous studies that have illustrated that MEFs show differential sensitivity to

drug-induced stresses activated by specific respiratory inhibitors. As a control, the genotypes were treated with the drug vehicle, DMSO. As markers of mitochondria quality control, we have employed Hsp60 for PQT and Atg5 for organellar quality control, mitophagy.

## DISCUSSION

Proteomic evolution due to domain acquisition can considerably modify protein function domain acquisition confers new proteome activities and modulates the arrangement of former domains. Results indicate that HtrA2 from mouse (*Mus musculus*) is on the same subgroup of the other rodent (*Rattus norvegicus*). Compared with other species analyzed in this research, both had the closest phylogenetic relationship with *Homo sapiens, Bos Taurus, Canis familiaris* and *Drosophila melanogsler.*

*Rattus norvegicus* analyzed in this research, had the closest phylogenetic relationship with *Homo sapiens*. Similar phylogenetic results were found in previous bioinformatic studies which have indicated that phylogenetically. Eukaryotic HtrA2 protein sequences correlate more to each other than to their bacterial homologues.[8,9]

In the present study, cells lacking CHOP, the transcription factor that intermediates the mitochondrial stress signaling, upregulation of Hsp60 following the treatments with ADEP4 and ACP5 is completely abolished the transcriptional activation of mitophagy as measured by the levels of Atg5 appears to be strongly affected by both loss of HtrA2 and loss of CHOP as shown by the absence of Atg5 upregulation by ADEP4 and Atg5 in the cell lines while the WT cells are showing the activation of this signaling pathway following the mitochondrial stress treatments.

In the current research, drug treatment with 6-OHDA in conjunction with ADEP4 or ACP5 have illustrated that these drugs might have a protective effect in ATP production of CHOP KO. When compared to the genotypes treated only with 6-OHDA, energy product ion was significantly less decreased in HtrA2/CHOP KO genotype treated in conjunction with ADEP4 or ACP5. Acyldepsipeptides (ADEPs) are effective antibiotics capable of impairing the activity of the bacterial protease, leading to bacterial cell death. ADEP4 inhibits the communication of ClpP with its ATPase associate by facing the same binding site and induces proteases to be opened and disrupted, proteins randomly, resulting in apoptosis (10) (11). Similar to ADEPs, ACP compounds are also capable to regulate the communication of proteases to its ATPases (12). Thus, treatment with ADEP4 and ACP5 recovered the detrimental effects of PD-like mitochondrial phenotypes in this model system. Genes that encode intracellular trafficking components are associated with common sporadic and familial forms of PD, as well as related syndromes that share some of the clinical features of PD. Most of these genes are known to affect trafficking to the lysosome in the context of late endosome-to-lysosome pathways, clathrin-dependent endocytosis, macroautophagy or mitophagy. Wild-type α-synuclein can also enter lysosomes through chaperone-mediated autophagy (Fig. 13).

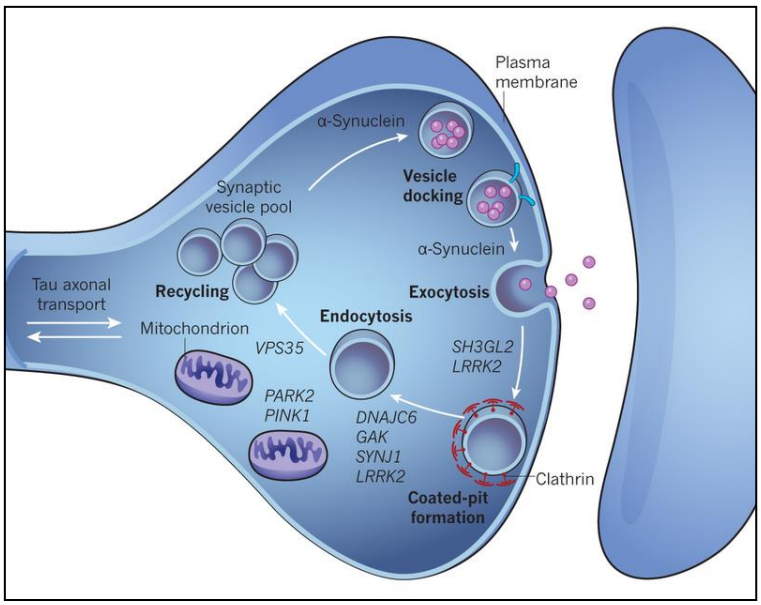


**Figure 13.** PD-related Genes Associated with Synaptic Vesicles Trafficking.

 

**Evidence Implicating Dopamine Deficit in Parkinson's Disease.**

- Parkinsonian symptoms induced by reserpine.
- Post-mortem depletion of dopamine in basal ganglia of PD (>80%).
- Parkinsonian symptoms induced by acute treatment of schizophrenic patients with neuroleptics.
- Parkinson's disease induced by MPTP; a neurotoxin destroying dopamine cells.
- PET scan shows loss of dopamine uptake in basal ganglia of living PD patients (Fig. 14).

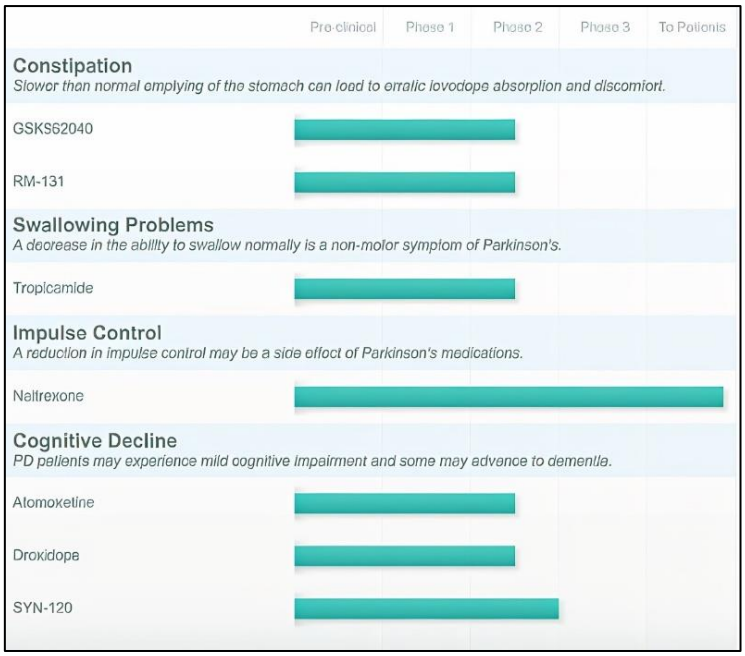


**Figure 14.** Different non-motor Side Effects Related to PD Dopaminergic Drugs Experienced During Clinical Trials of GSK962040, RM-131, Tropicamide, Naltrexone, Atomoxetine, Droxidopa and SYN-120.

## CONCLUSION

In summary, motor and non-motor symptoms as well as clinical signs of Parkinson's disease are; loss of balance and falls, stress and anxiety, uncontrollable movements, personalized treatments, dementia, mild thinking and memory problems, monitoring symptoms, sleep disturbances, dexterity and urinary problems. The present study concludes that HtrA2 and CHOP play a part in the transmission of stress signaling and the ensuing activation of mitochondrial quality control in Parkinson's disease.

Current therapy focused on compensating for dopaminergic signaling dysfunction treats symptoms, but does not protect neurons from death.

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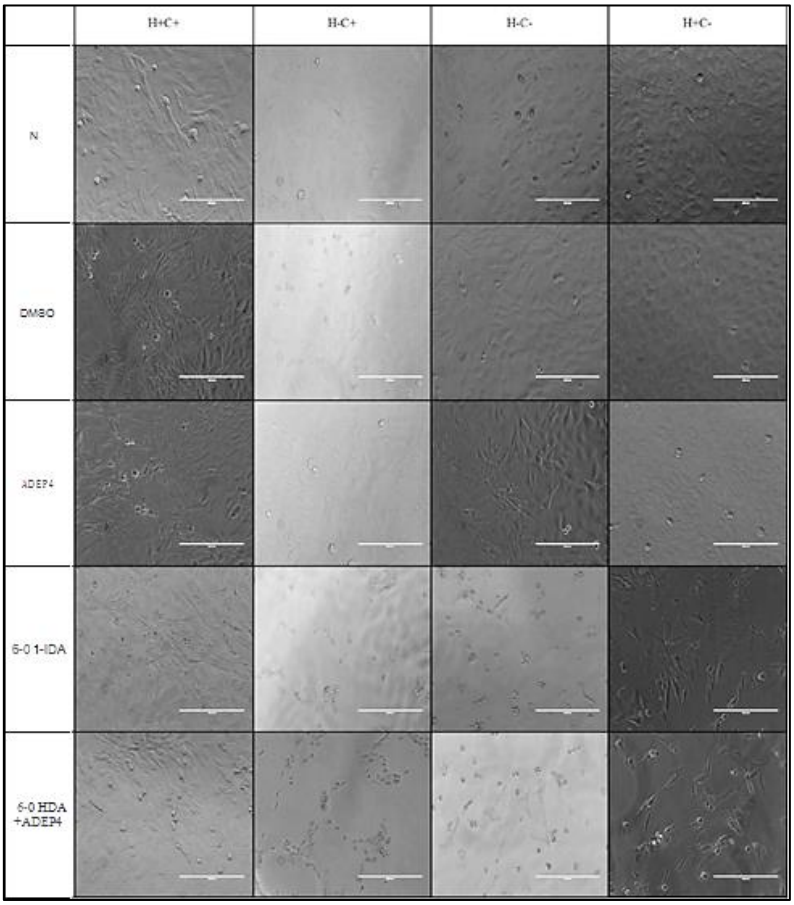
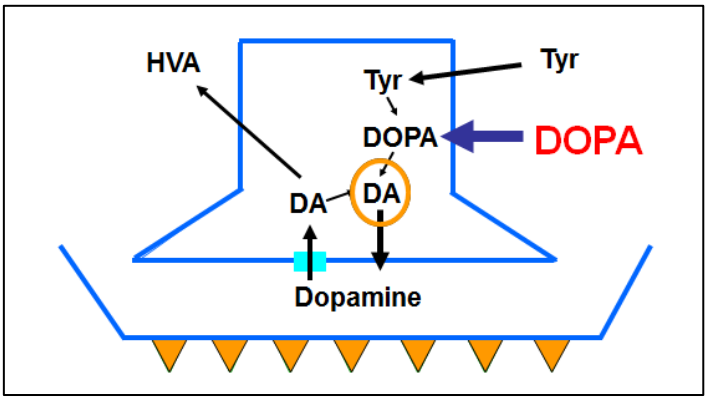
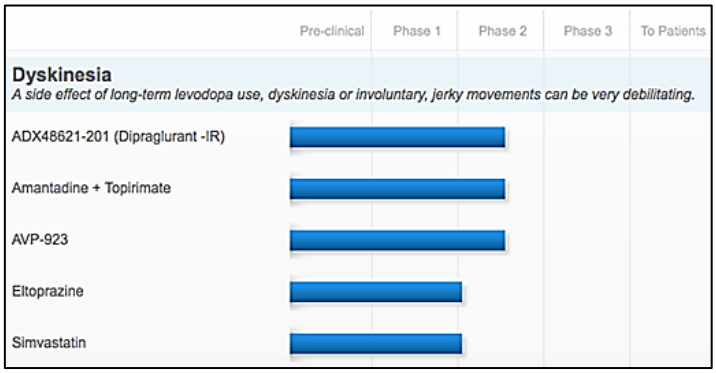



**Supplementary Figure 1.** Microscopy Visualization of Mice Embryonic Fibroblasts (MEFs) Obtained from Wild-type (WT), CHOP Knockout (KO) and HtrA2 KO Treated with 6-OHDA and ADEP4. Compared to the Other Drug Treatments, HtrA2/CHOP KO Genotype had Significantly Less Concentration of Alive Cells than the Well-treated Only with 6-OHDA. Drug Treatment with 6-OHDA in Conjunction with ADEP4 Significantly Improved Cell Survival.

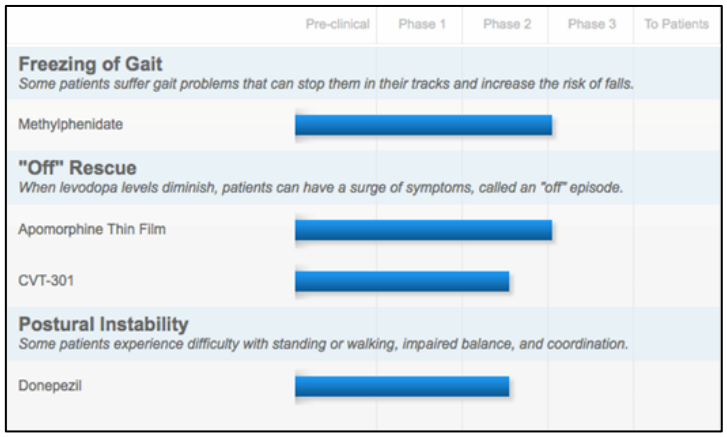
 




**Supplementary Figure 2.** DOPA Supplement Therapy in Parkinson's Disease.




**Supplementary Figure 3.** Comparison Between Medications Cause Bradykinesia as a Motor Side Effect Resulted From long-term of L-DOPA During Clinical Trial Process.




**Supplementary Figure 4.** Different Motor Side Effects Experienced During Clinical Trials of Methylphenidate, Apomorphine Thin Film, CVT-301 and Donepezil.

## CITE THIS ARTICLE

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