CRISPR in Parkinson's Disease

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What is Parkinson's Disease?

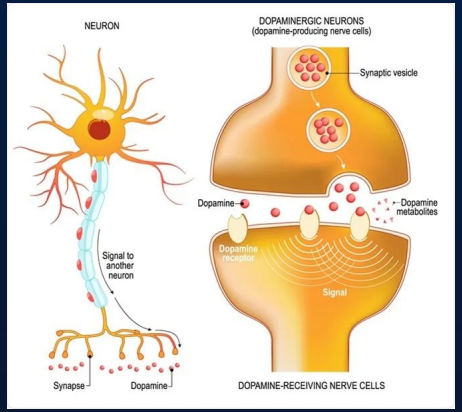
- Parkinson's Disease is a common Neurodegenerative disorder that is second to Alzheimer's Disease.
- Researches estimated that nearly 90,000 new cases of this disease are diagnosed in people ages 65 and older.
  - This is a 50% increase compared to the previous years
- This is a age related condition and as it affects the aging populations, Parkinson's puts a socioeconomic burden on healthcare systems and caregivers.

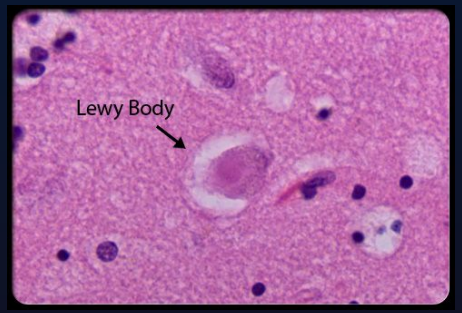
Symptoms of Parkinson’s Disease

- Parkinson’s is unique for every patient and sometimes it can be hard to see the early onset symptoms
  - Tremors in just one hand or sometimes a foot or the jaw
  - Stiff, Slow and rigid movement
  - Slurred, soft speech
  - Cognitive impairment
- There are no known cures for Parkinson’s

Biology Behind Parkinson's Disease

- Parkinson's affects a type of neuron called dopaminergic neuron.
  - These neurons are essential for voluntary and behavioral processes.
- Neurons communicate by releasing specific chemical signals called neurotransmitters.
- Dopaminergic neurons produce large amounts of neurotransmitters called dopamine.
- When these neurons degenerate in individuals with Parkinson's with time, the production of dopamine declines therefore causing motor dysfunction.
- Misfolded a-synuclein proteins, known as lewy bodies are common pathological determinants in Parkinson's.





Diagnosis and Testing for Parkinson's

- In a groundbreaking study, scientist have revealed a new tool to detect a Parkinson's biomarker in individuals who have not been diagnosed and may even be asymptomatic but has a high risk of developing the disease.
- Alpha- synuclein protein folds to form aggregates in parkinson's patients and can be detectable in the cerebrospinal fluid (CSF).
- Method is known as a-synuclein assay and it is based on the fluorescent detection of folded a-synuclein protein.
- The results from this study conducted in 1,123 individuals showed accurate detection of abnormal protein in 93 percent of participants with Parkinson's.
- The next steps in the assay development is to optimize it and be able to detect markers through a simple blood draw or nasal swab instead of a painful spinal tap.

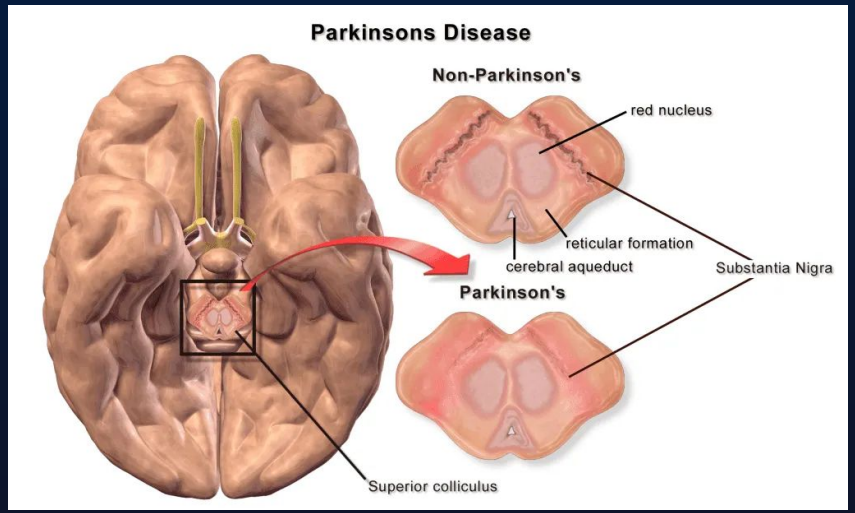
Treatment and Research: CRISPR

- CRISPR-Cas 9 can be well-utilized to screen genetic variants in Parkinson's to determine causality.
- CRISPR screening uses CRISPR as a tool to identify genes or genetic sequences governing specific morphological or physiological effects.
- CRISPR can be effectively used to study gene function in neuronal cell models.
- An example comes from Hoffman lab, they leveraged Synthego's genome editing potential to generate NADPH oxidase (NOX1, NOX2, and NOX4) knockout cell mode for Parkinson's.
- The study demonstrated the role of the Nox2 enzyme in oxidative stress-related degeneration, including α-synuclein accumulation, protein import impairment in mitochondria.

2P's of Parkinson's: *PINK1* and *PRKN*

- Aberrant mitochondrial pathways have been linked to neurodegeneration in Parkinson's.
- PTEN-induced Putative Kinase 1 (PINK1) and Parkin (E3 ubiquitin ligase) proteins work hand in hand through common pathways driving mitochondrial turnover and mitophagy
- Both these genes are often mutated in Parkinson's disease.

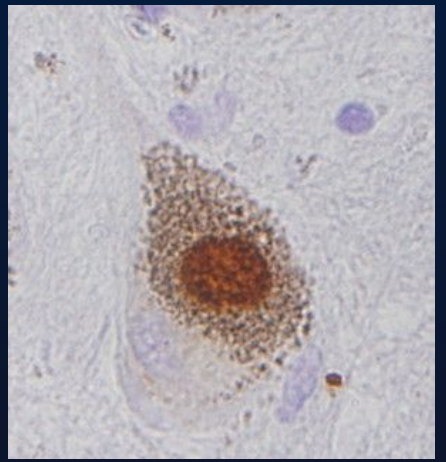
Using CRISPR-mediated *PINK1* Deletion in Non-human Primates



- Scientist used CRISPR/Cas9-mediated *PINK1* deletion, recapitulating the human parkinson's phenotype.
- They observed neuronal loss in the substantia nigra region in the midbrain of the affected animals.

The Alpha Factor: Alpha-Synuclein in Parkinson's

- Alpha-synuclein protein is abundant in dopaminergic neurons and is encoded by the *SNCA* gene.
- Insoluble aggregates of misfolded a-synuclein protein form lesions called Lewy bodies, which is a distinct pathologic feature in Parkinson's affected dopaminergic neurons.
- Mutations and multiplications in the *SNCA* gene have been linked to Parkinson's development and Progression.
- Researchers developed a novel platform using CRISPR-Cas9 to modify the *SNCA* gene with a bioluminescent tag and measure a-synuclein protein generation.



Altering the Epigenetic Landscape with CRISPR

- In addition to the genetic multiplication of *SNCA,* changes in the epigenetic landscape and the resulting regulation of *SNCA* gene expression can lead to excess a-synuclein protein in neurons.
- The common epigenetic alterations are histone modification, especially histone methylation.
- In a study published by the Kim lab at the University of Central Florida, researchers did a CRISPR-Cas9 approach to know the epigenetic regulation of the *SNCA* gene.
  - Using a histone demethylase as an “epigenetic eraser,” they were able to identify a specific histone modification regulating the *SNCA* gene.
  - This system was developed using neurons from patient derived stem cells.

Future Possibilities with CRISPR in Parkinson's Disease

- With the overwhelming success of CRISPR-Cas gene-editing systems in driving clinical research, there is immense hope for applications in Parkinson's and other neurodegenerative diseases.

- The Innovative Genomics Institute (IGI) at Berkeley, the University of California, San Francisco, and Genentech have now joined hands to form the Alliance for Therapies in
- The goal of this collaboration is to harness the power of CRISPR technology to study complex genetic interactions and molecular mechanisms underlying neurodegenerative disorders such as Parkinson's disease and hopefully treat them.

Question

Why would CRISPR technology be used in Parkinson's Disease and not other technology?

Reference

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- Mayo Foundation for Medical Education and Research. (2024, September 27). *Parkinson's disease*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055