Why do I have Parkinson's Disease

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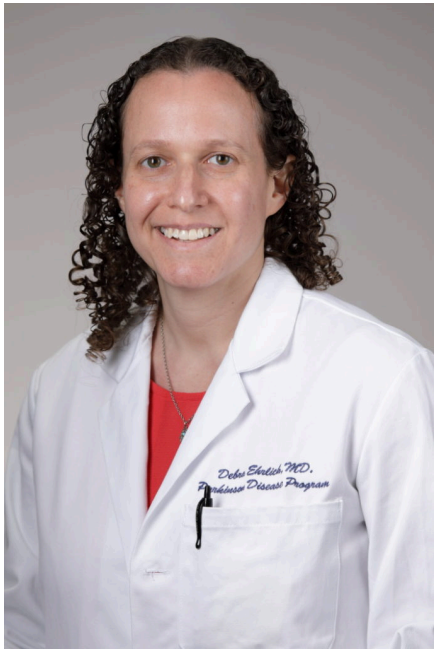

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Disclosures

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- Dr. Ehrlich receives grants for research in Parkinson's Disease from Medtronic, Inc
- The views presented in this presentation are my own and do not represent an official position of the National Institutes of Health or any other federal agency.

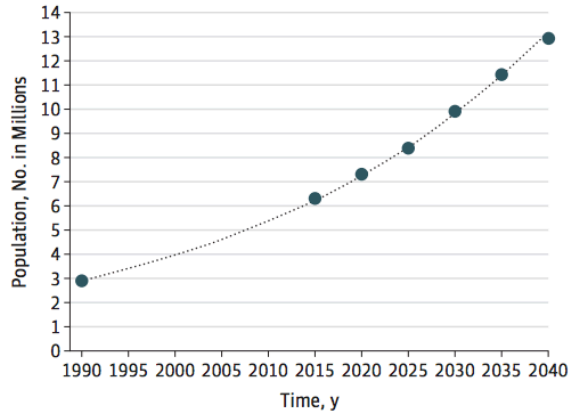
Outline

- Identify brain changes in PD
- Learn how PD symptoms correlate with brain changes
- Recognize potential causes and risk factors for PD
- Recognizes challenges in determining risk factors in PD
- Discuss recent research and treatment advances

Growing prevalence of Parkinson's Disease

- 2nd most common neurodegenerative condition
- Fastest growing neurological disease
- From 1990-2015 prevalence of PD more than doubled
- 6.2-6.9 million individuals with PD in 2015
- Projections using same growth rate predict 12.9 million affected by 2040
- Possible underestimate of future burden

Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040



Sources: Global Burden of Disease Study (1990 and 2015) and projections based on published[2] and public[3] sources.

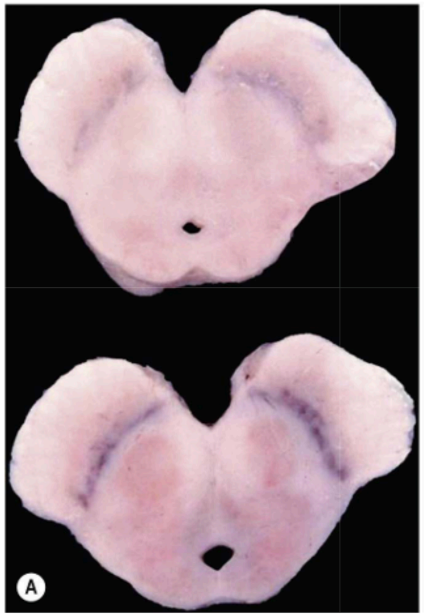
Dorsey ER & Bloem BR (2018), JAMA Neurol

Why do I have Parkinson's Disease

About 90% of cases do not have an identified cause…yet

What happens to the brain in PD?

- PD is caused by impairment or death of dopamine producing neurons in a deep part of the brain called the substantia nigra
- The substantia nigra controls how you move your body
- Dopamine is an important chemical messenger in the brain
- Decrease in brain dopamine levels causes abnormal brain activity
- Therefore, loss of dopamine in the area of the brain that controls movement causes movement problems in PD



What else happens to the brain in PD?

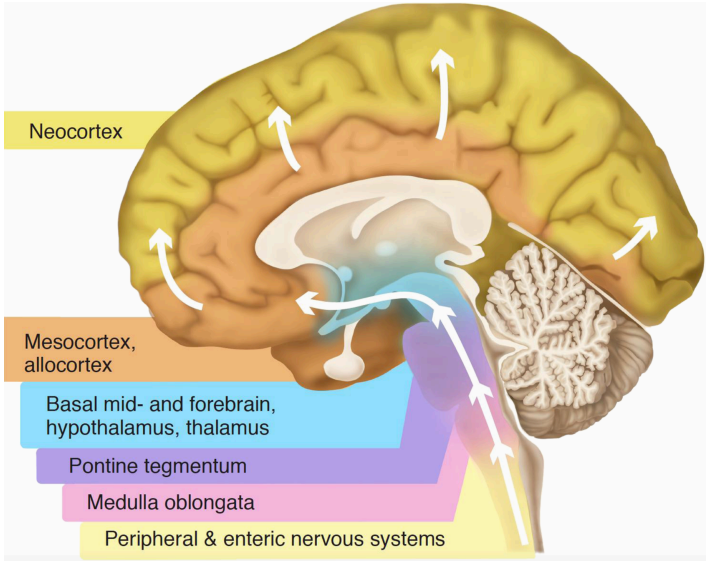
- Other types of neurons in other regions of the brain are also affected
- Loss of pigmented neurons of the locus coeruleus which contain norepinephrine
- Serotonergic neurons in the raphe of the pons and medulla
- Cholinergic frontal and brainstem regions

What is a Lewy Body?

- Alpha-synuclein is a protein abundant in the human brain
- The normal role of alpha-synuclein is unknown
- Abnormal alpha-synuclein takes an abnormal shape that causes it to clump
- These abnormal clumps of protein accumulate in neurons and are called Lewy Bodies
- Lewy bodies are an important pathological finding in brains of people with Parkinson's disease, as well as some other neurologic conditions

Braak Staging Hypothesis and Challenges

A theory that describes how alpha-synuclein and Lewy Body pathology might spread throughout the brain in PD



Visanji et al (2013) Acta Neuropathologica

Other challenges to the model

- Is the Lewy Body harmful or protective?
- The presence of Lewy Bodies in brain regions prone to neurogeneration suggested that it was detrimental to neuronal survival
- Lewy bodies might be a protective cellular mechanism to sequester toxic alpha-synuclein aggregates and even aid in their degredation

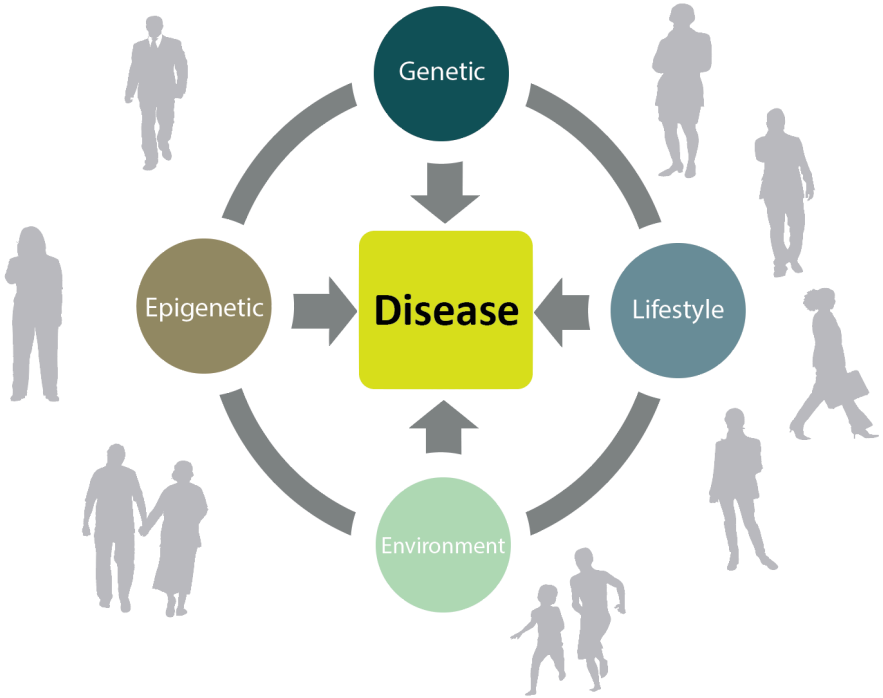
Premotor symptoms of PD

- Impaired sense of smell---olfactory nerves
- Constipation—nerves of the GI tract
- REM sleep behavior disorder: brainstem

What causes loss of dopamine neurons in PD?

- Unfortunately, scientists have not yet conclusively answered this question
- However, we do know that many factors can contribute to the risk of getting PD

Many factors contribute to risk of PD

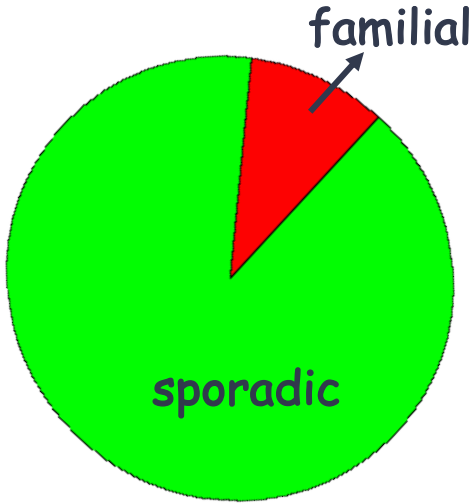


Intrinsic risk factors for PD

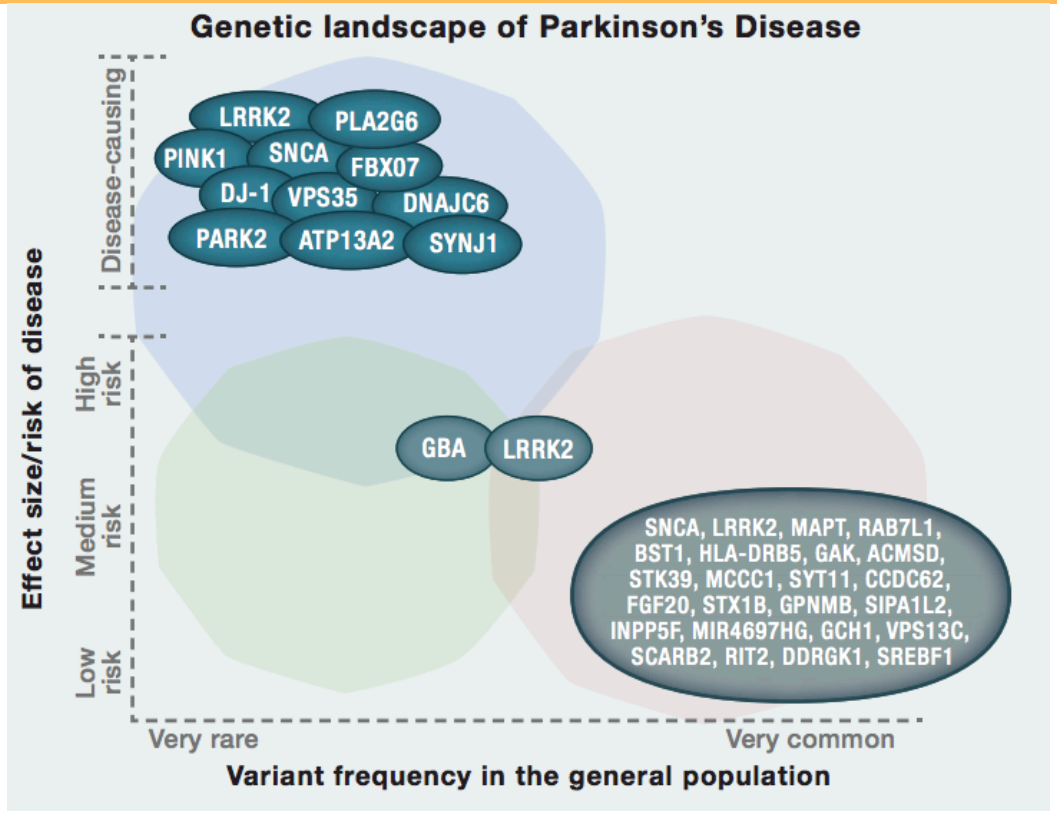
- Genetics
- Epigenetics
- Age
- Sex
- Gut microbiome

Genetics

- The risk of Parkinson's disease can be inherited
- About 10% of people with PD have a positive family history and a clearly defined genetic cause
- About 90% of cases of PD are "sporadic"
- Genetics do play a role in sporadic PD



Spectrum of Genetic risk in PD



Bras J, Guerreiro, R, Hardy J (2015) Cell

Epigenetics

- A large portion of the heritability in PD is not explained by genetics alone
- Epigenetics is the study of changes in gene activity that are not caused by changes in the DNA sequence itself
- Rather, these changes are in the way the genes are expressed or the way they exert their effects
- Chemical modifications can turn on or turn off genes
- Epigenetic modifications can change over the lifetime of an individual

Age

- Age is the largest risk factor for PD
- Exact cause is unknown
- Suggested theories include the fact that pathology of the substantia nigra is common in older persons and may contribute to motor impairment in old age

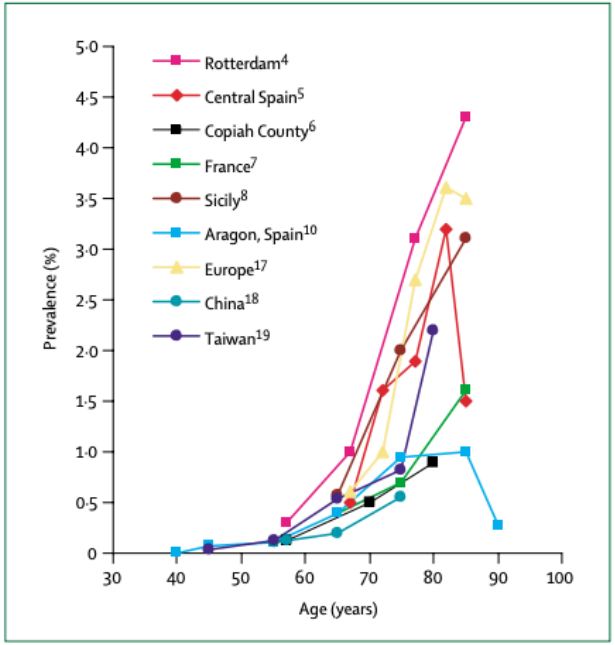
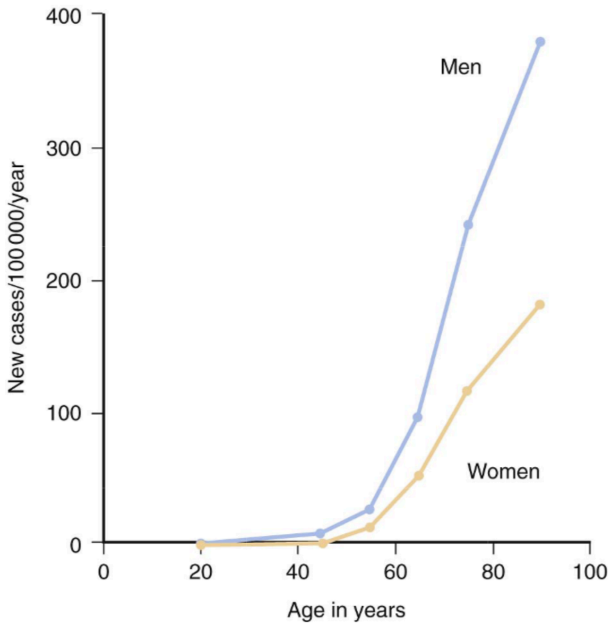


Figure 1: **Population-based prevalence studies of Parkinson's disease**

De Lau & Breteler, Lancet Neurol 2006

Sex

- Men have a higher risk of PD than women
- Studies vary on M:F ratios, men ~1.5x more likely than women
- Exact reasons for this difference are unclear
- Theories include:
  - -hormonal differences
  - -differential exposures



Bower JH et al (2000) Mov Dis

Gut microbiome

- Trillions of microorganisms are located in the human GI tract; this is collectively called the “microbiome”
- Both “good” and “bad” bacteria are part of the microbiome
- People with PD demonstrated significantly altered intestinal microbial compositions compared to healthy controls
- Evidence also suggests differences in oral and nasal microbiota
- Causal link with PD not yet established

Jackson et al, 2019, Front Neurol

External risk factors

- Environmental exposures
  - -Chemicals
  - -Pesticides
  - -Well water
- Diet and habits

Chemical Exposure

- MPTP, a component of synthetic heroin in early 1980s
- Caused rapid onset, permanent parkinsonism with virtually all the same motoric and non-motoric symptoms as PD
- Patients responded well to levodopa
- Used to create an animal model of PD
- Animal models showed loss of dopaminergic neurons in the substantia nigra

Pesticides

- Substantial evidence suggesting that pesticide exposure increases risk of PD
- Risk associated with specific compounds is uncertain
  - Rotenone, paraquat
- PPE can reduce risks associated with occupational exposure
- Challenges: co-exposures in same participants

Well water

- Some studies showed higher rates of PD in people who drank well water
- More recent studies showed no association
- Compounds in private well water are not tested
- Risk may actually be attributed to pesticides

The Challenge in Searching for Environmental Risk Factors

- Late onset sporadic PD takes decades to develop
- Prolonged prodromal phase
- Causative exposures may occur decades before clinical diagnosis
- Once neurodegeneration has started, many environmental and genetic factors may come into play to modify PD progression during prodromal development

Another Challenge: Complexity of the "Environment"

- Chemicals
- Bacteria and viruses
- Climate
- Lifestyle
- Socioeconomic conditions
- Interactions between host and environment

Additional Challenges

- PD involves multiple body systems and organs
- Potential multiple routes of entry for environmental exposures
- Multiple susceptibility windows

Diet and Habits

- Coffee, Tea, Caffeine
- Tobacco smoking
- Diet

Coffee and Tea

- Numerous studies have shown a lower risk of PD among regular coffee drinkers as compared to non-drinkers
- Some studies demonstrated a dose response effect
- Studies have shown lower risk of PD among tea drinkers vs non-drinkers
- Neuroprotective effects of caffeine have been demonstrated in mouse models of PD

Ascherio & Schwartzchild, 2016, Lancet Neurol

Smoking

- Low PD risk among tobacco smokers reported in several studies
- Similar results with chewing tobacco
- Nicotine neuroprotective in animal models of PD

Ascherio & Schwartzchild, 2016, Lancet Neurol

Diet

- High saturated fat: ↑ risk of PD
- Mediterranean diet: ↓ risk of PD
- Dairy: ? ↑ risk of PD
- Gut microbiome

Medical History and comorbid diseases

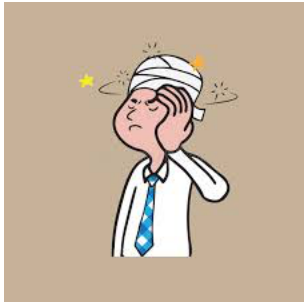
- Diabetes
- Head injury
- Hepatitis C

Diabetes

- Several studies have shown an increased risk of PD in individuals with DM2, however several other studies have demonstrated no association
- Conflicting results suggest complex relationship between insulin resistance and PD, which may be modified by other factors
- PD risk among individuals with DM could be reduced by the use of antidiabetic drugs

Traumatic Brain Injury

- TBI is relatively frequent (2.87 million people annually)
- Some studies have suggested that TBI is associated with an increased risk of subsequently developing PD
- Study biases (recall bias, frequency of falls in early PD) may confound the data
- However, a recent large study did not support the association
- Timing after injury and/or reverse causation may account for opposing findings



Hepatitis C

- Some studies have shown a positive association between Hepatitis C and PD, while other studies have indicated no association
- A recent study showed that while chronic hepatitis C infection was associated with increased risk of parkinsonism or PD, patients receiving treatment for hepatitis C infection had a reduced risk
- HCV may induce 60% dopaminergic neuron death in rats and may release inflammatory cytokines that participate in the pathogenesis of PD
- Both HCV and PD share overexpression of inflammatory biomarkers

The balance of PD risk factors

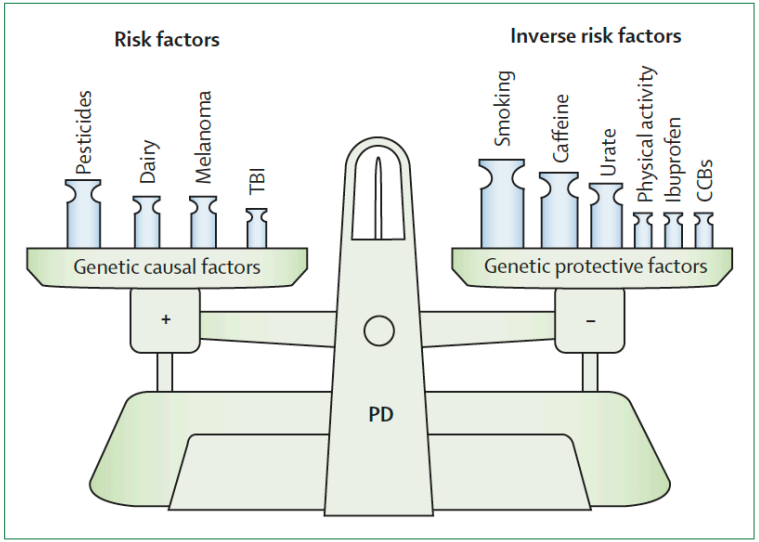


Figure 4: **The balance of genetic and environmental factors that underlie Parkinson's disease occurrence**

Larger weights have been used for those factors with stronger epidemiological evidence. We have included only factors supported by multiple prospective studies, but the presentation is not exhaustive and it is meant only for illustrative purposes. Factors included might or might not be causal. TBI=traumatic brain injury. PD=Parkinson's disease. CCBs=calcium channel blockers.

Ascherio & Schwarzchild, Lancet Neurol, 2016; 15; 1257-72

New directions for therapeutics

- Therapies targeting alpha-synuclein
- Precision medicine

Why is alpha-synuclein an attractive target for potential treatments?

- Mutations in the SNCA gene (the gene encoding a-syn) cause autosomal dominant PD
- Genetic variants at the SNCA locus are risk factors for sporadic PD
- A-syn is the major component of Lewy Bodies (a pathological hallmark of PD)

Therapies to target alpha-synuclein

Targeting of abnormal alpha-synuclein

- Antibodies against a-syn
- Vaccine: prompts the body to produce antibodies against a-syn
- Preventing a-syn clumping
- Inhibiting translation or transcription of the SNCA gene (ASOs, siRNA)
- Enhance enzymatic or lysosomal clearance of intracellular a-syn

Genetically based therapeutics

- LRRK2 kinase inhibitors

- GBA mediated mechanisms
  -Increased lysosomal GaCase activity-ambroxol
  -Modulation of GBA related glycophingolipids-Inhibition of biosynthesis of lipid substrates, thereby inhibiting their accumulation

Summary

- For the majority of PD cases, the exact cause is still unknow
- Most likely, the risk of PD is influenced by a complex interaction between many different factors
- Researchers are making progress in better understanding some of the causes and risk factors for PD, which is leading to major advantages in potential treatments

Thank You