What Causes Parkinsons Disease?
Environment, Genetics, and Beyond

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Comprehensive Parkinsons Disease Care, 3/26/2023

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1

Objectives

1. [Briefly] describe the pathophysiology and pathogenesis of Parkinsons Disease
2. Recognize environmental risk factors and protective factors
3. Identify the genetic causes of PD

2

Disclosures

Clinical Deep Brain Stimulation training – Medtronic – 2021

3

What Causes Parkinsons Disease?

Long story short:
It's very complicated and we don't know!

4

Epidemiology – Who Gets PD?

Incidence: 6-35/100,000 new cases annually

- Increases significantly with age: 9th decade 5-10x higher than 6th decade

Prevalence: Estimated 6.2 million cases globally in 2015

- 45-55 years of age: <1%
- >85 years: ~4% of men, ~2% of women

Average age of onset: 65

Affects men greater than women, 3:2

Primarily sporadic: only 10-15% of cases have a family history (1st degree relative)

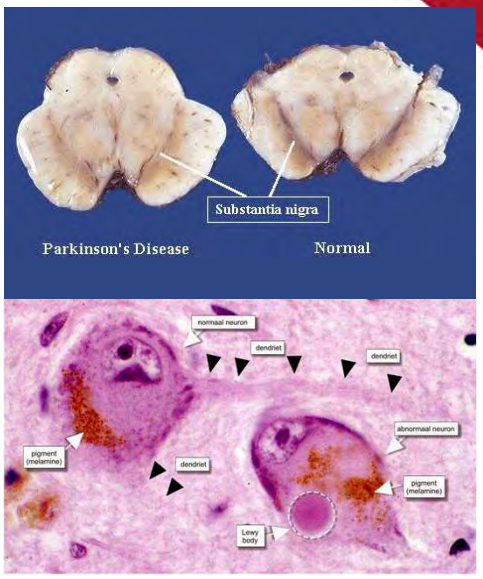
Simon DK, Tanner CM, Brundin P. Clin Geriatr Med. 2020 Feb

5

Neuropathology

PD is classically pathologically characterized as:

- Degeneration of dopaminergic neurons in the substantia nigra
- Presence of intraneuronal aggregates called Lewy Bodies and Lewy Neurites



Kon T, Tomiyama M, Wakabayashi K. Neuropathology of Lewy body disease. Neuropathology. 2020 Feb

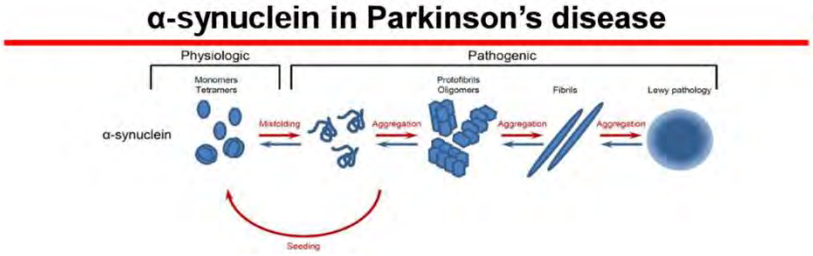
6

Neuropathology

Lewy bodies are primarily composed of a protein called alpha-synuclein

α-synuclein is heavily expressed in neuronal tissue. Thought to be integral for vesicular trafficking and neurotransmitter release

In PD, protein misfolding results in abnormal aggregation that becomes insoluble and eventually leads to build-up in neurons to toxic effect



Kalia . Parkinsonism Relat Disord 2019;59:215

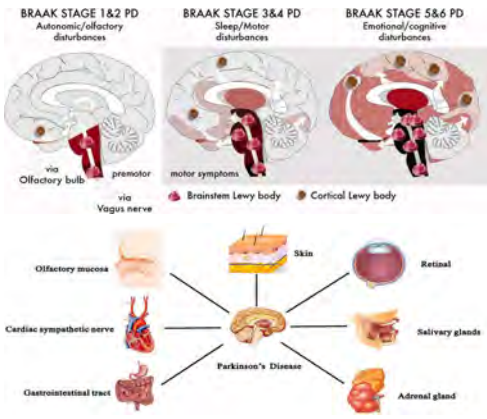
7

Widespread Lewy Body Deposition

In 2003, pathologist Helios Braak demonstrated widespread cerebral Lewy Body deposition in PD patients, roughly correlating with disease severity

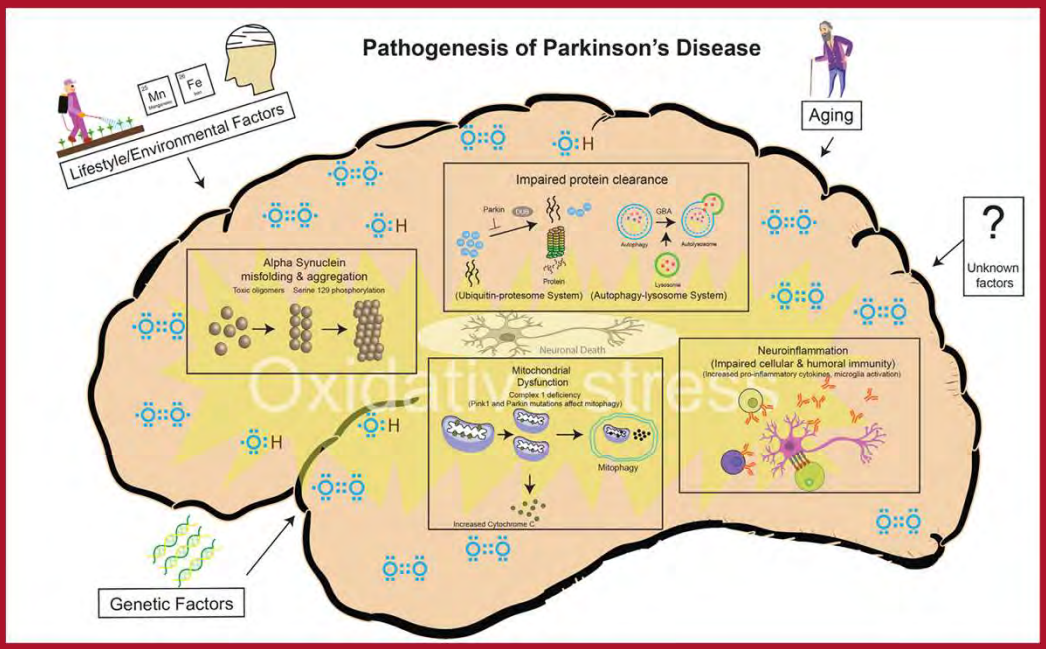
An unknown pathogen is inhaled and swallowed, leading to α-synuclein misfolding in nose and gut neurons, which spreads to the brainstem via the olfactory and vagal nerves

Alpha-synuclein aggregation has also been demonstrated throughout the body in peripheral nerves



Braak H, et al. Neurobiol Aging. 2003 Mar-Apr
Ma LY, et al. ACS Chem Neurosci. 2019 Feb

8



Jankovic J, Tan EK. J Neurol Neurosurg Psychiatry. 2020 Aug

9

Modifiable Risk Factors

10

First, a word about risk factors...

Many studies over the years investigating environmental risk factors, often with conflicting results.

Statistical risk ≠ cause

11

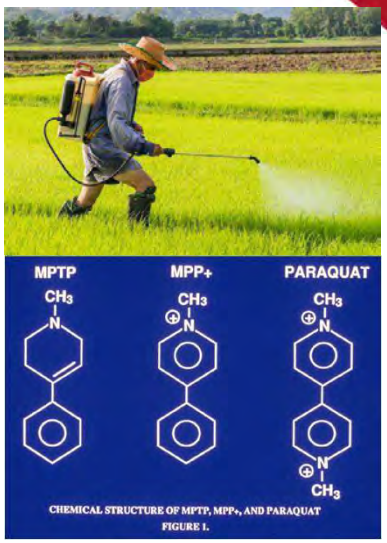
Pesticides/Solvents

A 2013 meta-analysis of 104 studies found that exposure to ANY pesticide, herbicide, or solvent raises risk, OR 1.8 overall

Thought to lead to mitochondrial dysfunction

Certain pesticides and solvents have higher risk, and some have been shown to induce Parkinsonism in animal models. PPE (gloves, mask) use modifies risk

- Paraquat – OR 2.2
- Rotenone
- 2,4 – Dichlorophenoxyacetic acid (Agent Orange) - OR 1.0-1.8
- Organochlorides
- Dithiocarbamates – Maneb/mancozeb OR 2.2



Pezzoli G, Cereda E. Neurology. 2013 May
Furlong M, et al. Environ Int. 2015 Feb

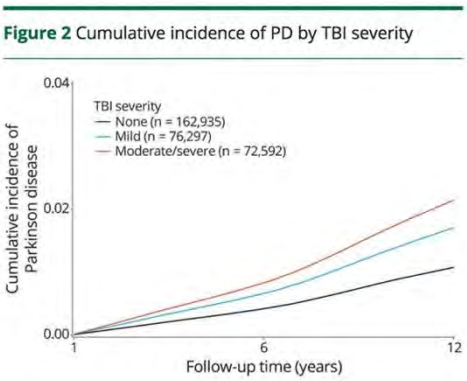
12

Head Injury

Meta-analysis of 22 studies in 2013 showed a pooled OR 1.57

Consortium study in 2018 of 325,870 patients confirmed an association between PD and TBI

- Mild – OR 1.56
- Moderate/severe - OR 1.83



Jafari S, et al. Mov Disord. 2013 Aug
Gardner RC, et al. Neurology. 2018 May

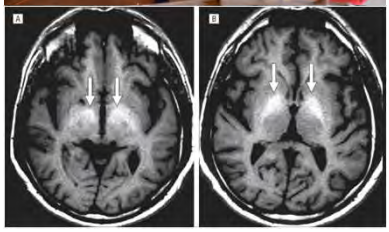
13

Heavy Metal Exposure

Manganese-induced Parkinsonism has been known for many years, affecting welders and manganese miners

A 2017 study found a correlation between estimated manganese exposure and severity of PD symptoms

Characteristic MRI finding of T1 hyperintense basal ganglia. Often results in a characteristic phenotype with high-stepping gait, symmetric symptoms, and less tremor



Racette BA, et al. Neurology. 2017 Jan

14

Estrogen exposure

Multiple studies show bilateral salpingo-oopherectomy increases PD risk

Increased risk of developing PD with esterified estrogen use OR 6.9

No risk with conjugated estrogen use

Parker WH, et al. Obstet Gynecol. 2017 Jan
Lundin JI, et al. Mov Disord. 2014 Nov.

15

High Dairy Intake

Associated with modest risk

Meta-analysis in 2017 found:

- Total dairy intake – no risk
- Low fat dairy intake >3 servings/day - OR 1.34

Hughes KC, et al. Neurology. 2017 Jul

16

Protective Factors

Cigarette use – OR 0.39
- Consistent inverse dose-response
- Not explained by selective survival of non-smokers

Caffeine
- High coffee intake – RR 0.43
- Tea – OR 0.85

Ibuprofen – RR 0.62. No effect with other NSAIDs

Exercise – HR 0.66, comparing >6 hours/week of activity to <2 hours/week

Belvisi D, et al. Neurobiol Dis. 2020 Feb

17

Genetics of Parkinsons Disease

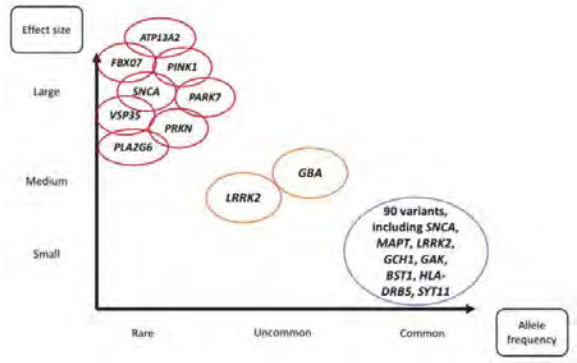
Long-thought to be a strictly acquired condition

Now thought to be complex disease with both genetic and environmental contributions
- Discovery of the first pathogenic mutation in an Italian PD kindred in 1981 (*SNCA*)
- Long-duration twin studies confirmed higher incidence in monozygotic twins vs. dizygotic twins

Family history confers 3-4x risk of developing PD

Goldman SM, et al. Ann Neurol. 2019 Apr

18



Genetics of Parkinsons Disease

Only 10-15% of cases of Parkinsons are familial

5-10% of PD patients have an identifiable pathologic genetic mutation that is known to cause/contribute to disease

The presence of a mutation does not necessarily confer disease. Some genes have high penetrance, but most mutations have low-medium penetrance

Day JO, Mullin S. Genes (Basel). 2021 Jun

19

Monogenic PD

A group of genes with mutations leading to Parkinsonism with high-penetrance

Often early-onset (age <50) and with atypical features (early dementia, poor response to levodopa, pyramidal signs, severe dystonia)

Rare

Gene (HGNC Approved Name)	Alternative Gene Names	Inheritance	Pathogenicity	PD Phenotype	Function
SNCA	*PARK1, PARK4, NCAP*	AD	Pathogenic	Early-onset	Uncertain (encodes α-synuclein)
VPS35	*PARK17, MEM3*	AD	Pathogenic	Typical	Retromer and endosomal trafficking
PINK1	*PARK6*	AR	Pathogenic	Early-onset	Mitochondrial
PARK7	*DJ-1*	AR	Pathogenic	Early-onset	
PRKN	*PARK2, PARKIN*	AR	Pathogenic	Early-onset	
PLA2G6	*PARK14, IPLA2*	AR	Pathogenic	Early-onset, atypical	Cell membrane
ATP13A2	*PARK9*	AR	Pathogenic	Early-onset, atypical	Lysosomal
FBXO7	*PARK15, FBX7*	AR	Pathogenic	Early-onset, atypical	Mitochondrial
POLG	*POLG1, POLGA*	AD	Pathogenic	Early-onset, atypical	Mitochondrial DNA maintenance
DNAJC6	*PARK19, DJC6*	AR	Likely pathogenic	Early-onset	Synaptic vesicle formation and trafficking
DNAJC13	*PARK21, RME8*	AD	Conflicting reports	Typical	
TMEM230	*C20ORF30*	AD	Conflicting reports	Typical	
SYNJ1	*PARK20*	AR	Pathogenic	Early-onset, atypical	
VPS13C	*PARK23*	AR	Pathogenic	Early-onset	Mitochondrial
CHCHD2	–	AD	Pathogenic	Typical	Uncertain
DCTN1	–	AD	Pathogenic	Atypical	Microtubule

Day JO, Mullin S. Genes (Basel). 2021 Jun

20

LRRK2

Physiologic role of *LRRK2* is thought to be related to autophagy, mitochondrial function, and microtubule stability

The most common "monogenic" cause of PD

- Most common variant: 5-6% of all familial cases, and 2% of all sporadic cases
- Expressed most highly in Ashkenazi Jew and North African Berber populations

The highest penetrant variant has a 25-75% risk of developing PD by age 80

Phenotype is very similar to typical, idiopathic Parkinsons Disease

Simpson C, et al. Parkinsonism Relat Disord. 2022 May

21

GBA

Function of *GBA* is essential to lysosomal function and glycosphingolipid homeostasis

The most common genetic risk factor for PD

- Present in 5-15% of all PD patients
- Does NOT cause a Mendelian form of inheritance, raises lifetime risk by 2-4x

Phenotype is similar to typical, sporadic PD

Homozygous GBA mutation causes Gaucher Disease

Smith L, Schapira AHV. Cells. 2022 Apr.

22

Genetic Testing

When should I consider an underlying genetic Parkinsons Disease?

- Strong family history (1st degree relatives, multiple 2nd degree relatives in an AR pattern of inheritance)
- Young-onset (<50 years old)
- Atypical features: early dementia, severe dystonia, upper motor neuron signs (hyperreflexia, weakness, spasticity)

23

Genetic Testing – Should I Get it?

A decision reached between patient and provider

Things to consider:

- Outcome rarely affects treatment, no gene-specific therapies (for now)
- May help determine a more accurate prognosis for future life planning
- May facilitate participation in research trials
- Risk to next generation

Consider a referral to a genetic counselor before committing to testing

24

Ordering Genetic Testing

PDGeneration – Free genetic testing for PD patients and family members. Research study through Indiana University. [PDGeneration.com]

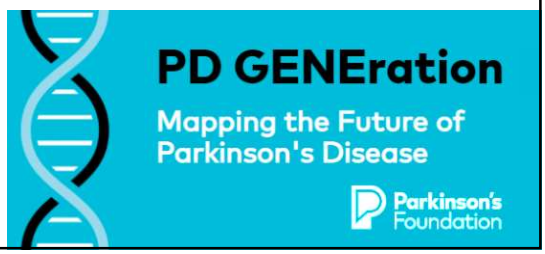
- Only tests for variants in 7 genes: *GBA*, *LRRK2, PRKN, SNCA, PINK1, PARK7* (*DJ-1*) and *VPS35*.

Invitae – Hereditary Parkinsons Disease and Parkinsonism Panel

- 26 genes. Works well with insurance. Max OOP cost $250

GeneDx – Parkinsons Disease Panel

- 46 genes



25

Summary

Parkinsons Disease is a complex disease with both genetic and environmental contributions

The underlying cause is thought to be related to toxic accumulation of proteins leading to mitochondrial dysfunction and neuroinflammation that ultimately leads to neuronal death

Modifiable risks factors: pesticide/solvent exposure, head trauma, heavy metal exposure, estrogen use and possibly low-fat dairy

Protective factors: cigarette use, caffeine use, exercise, possibly ibuprofen

PD is primarily sporadic, only 10-15% of cases have family history

Pure genetic causes of PD are uncommon

- *LRRK2* has the most common genetic variant causing familial PD
- *GBA* mutations are the most common genetic risk factor for PD

26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27