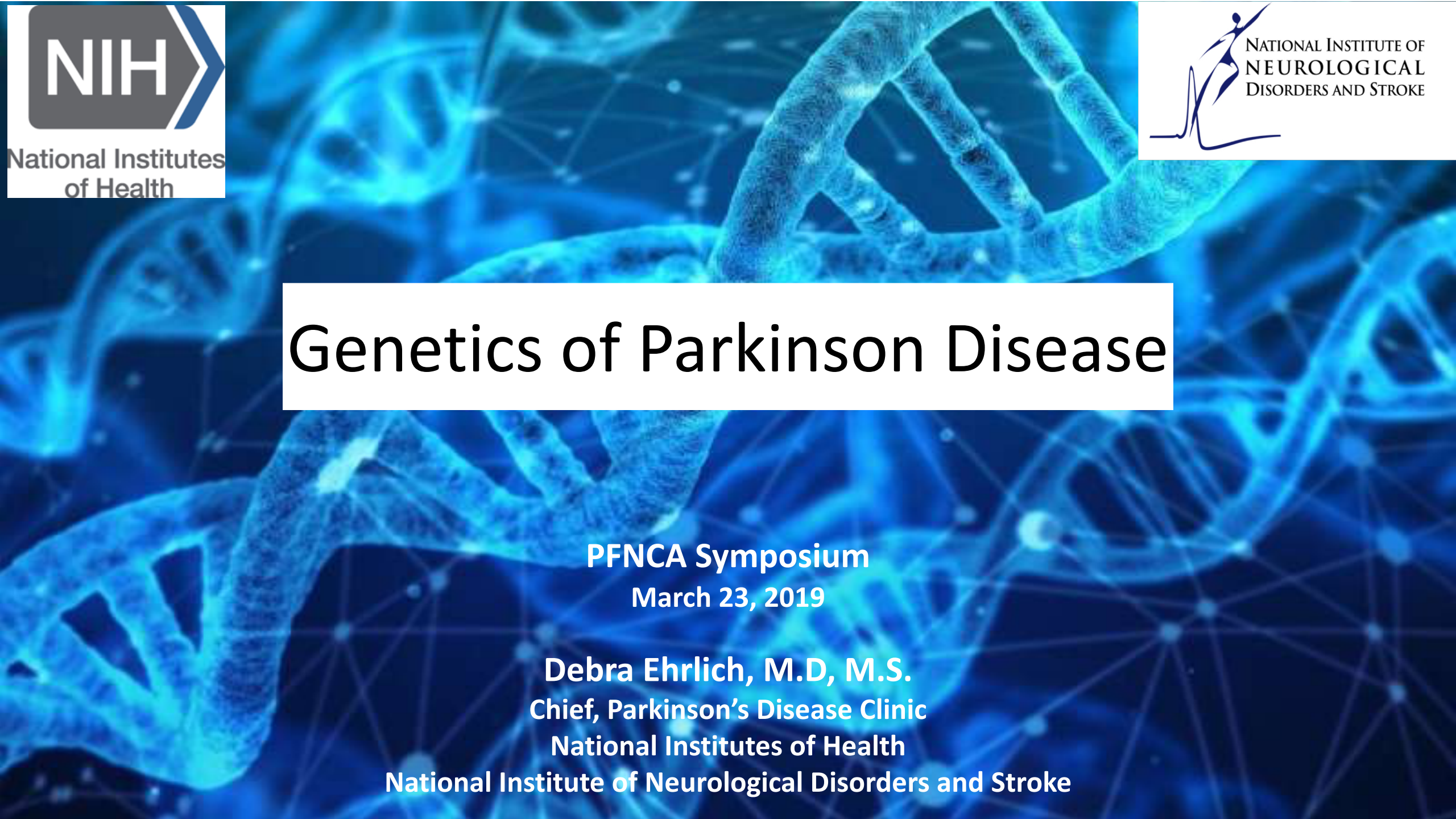

Genetics of Parkinson Disease

PFNCA Symposium
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Disclosures

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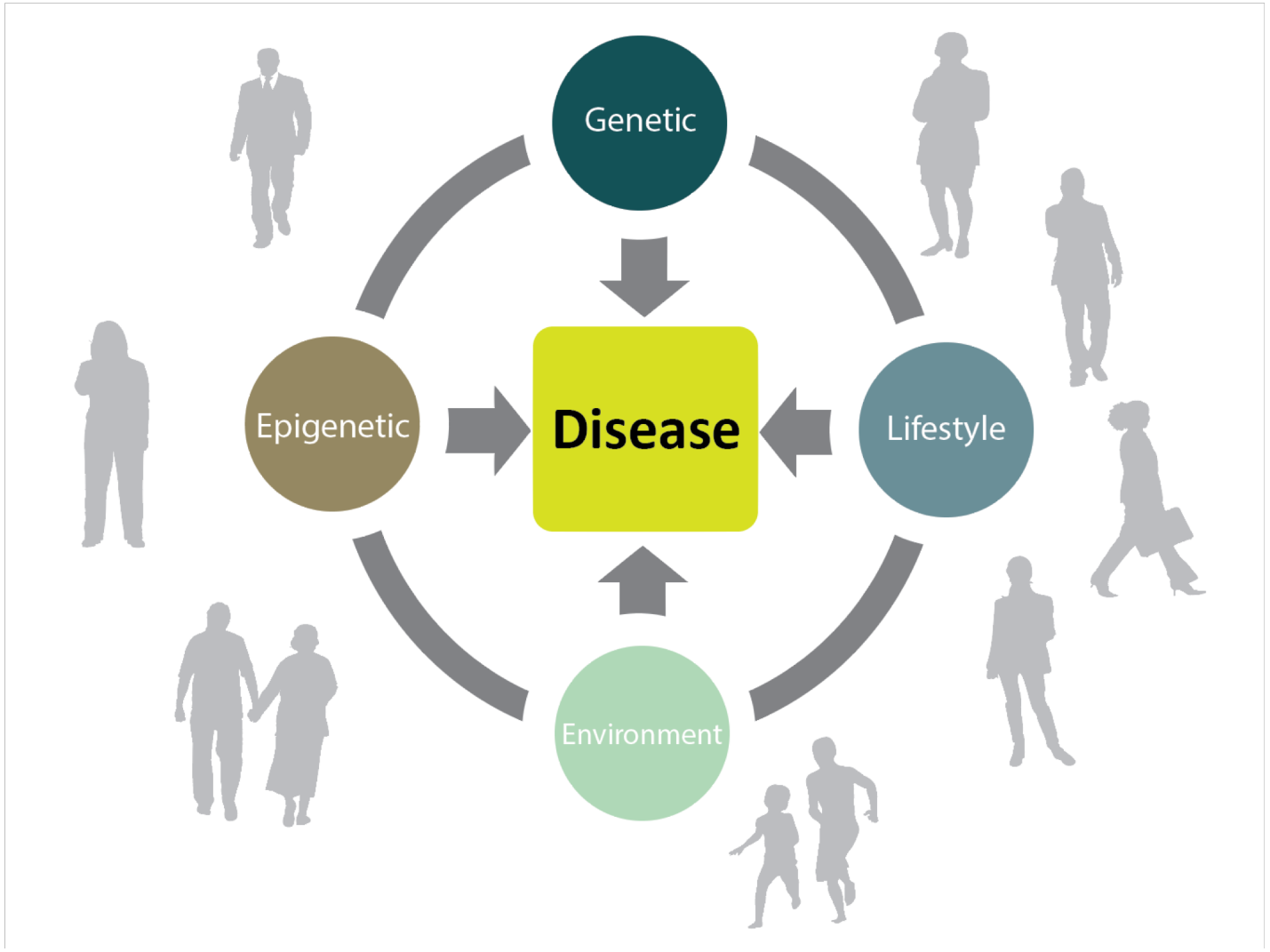
- Dr. Ehrlich receives grants for research in Parkinson's Disease from Medtronic, Inc

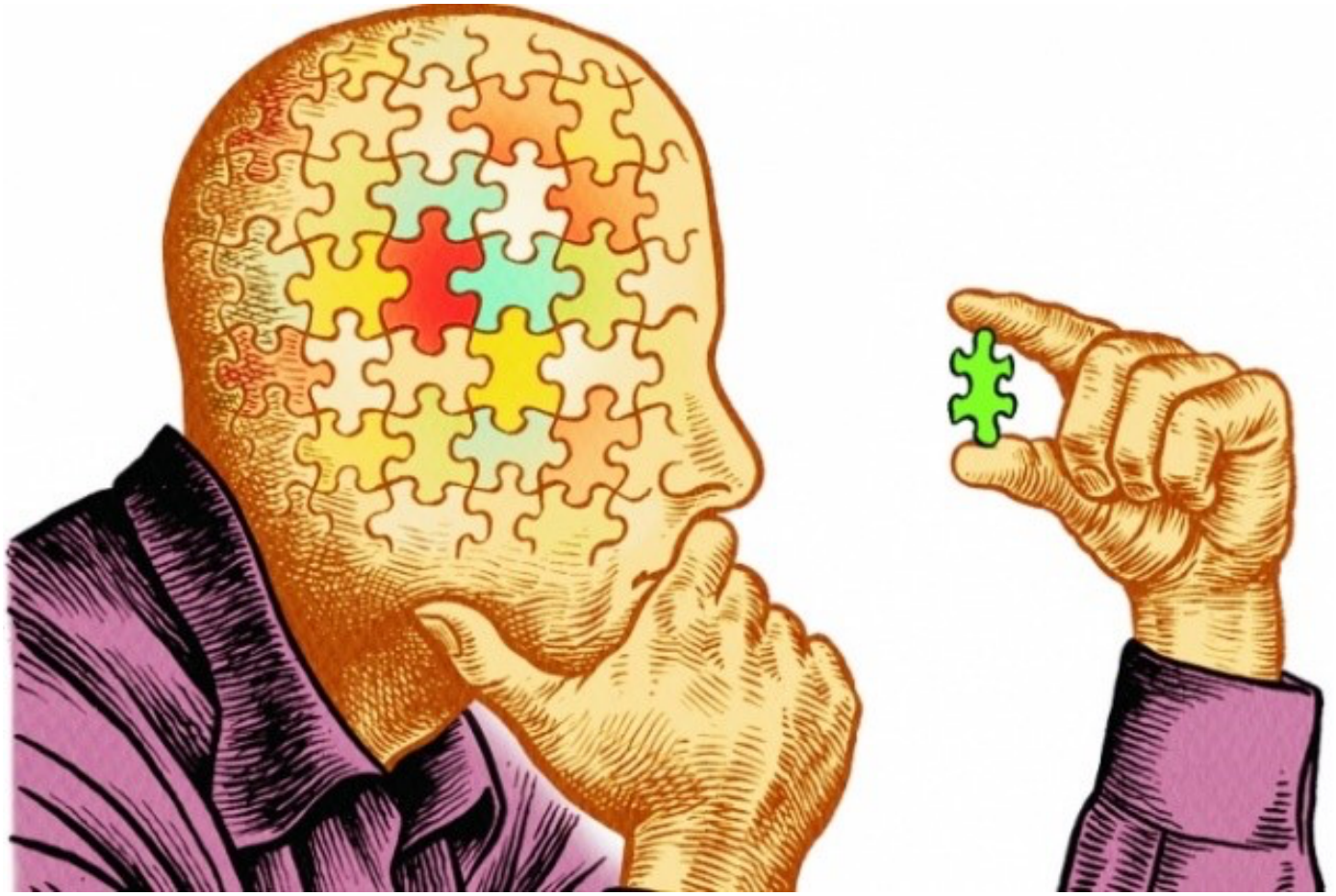
Outline

- Introduction
- Review basic genetics
- Genetics of PD
- Future uses of genetics in PD
- Is genetic testing right for you?

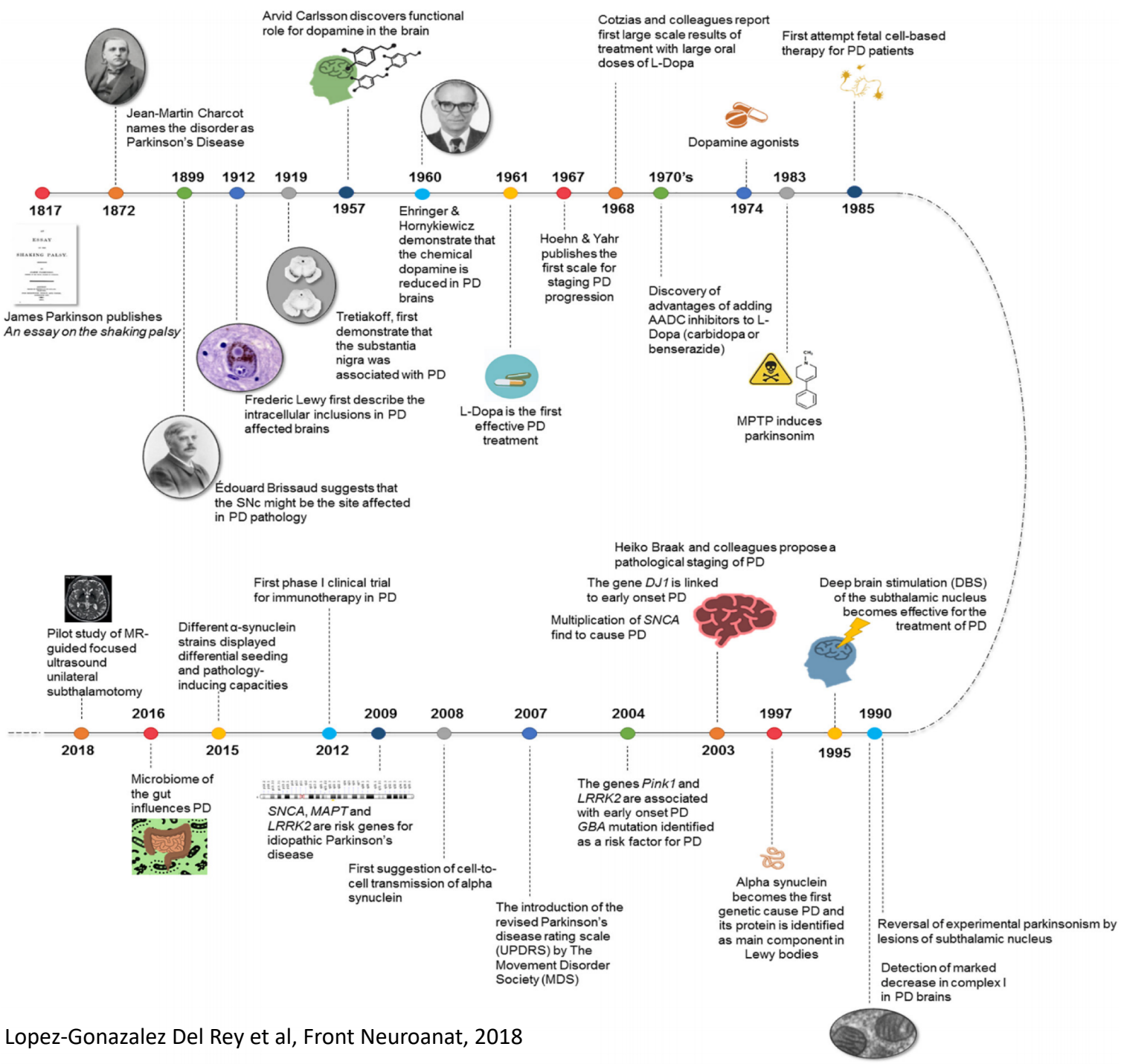
Complex Disease



Genetics is only a piece of the puzzle



Historic Breakthroughs in Parkinson's Disease

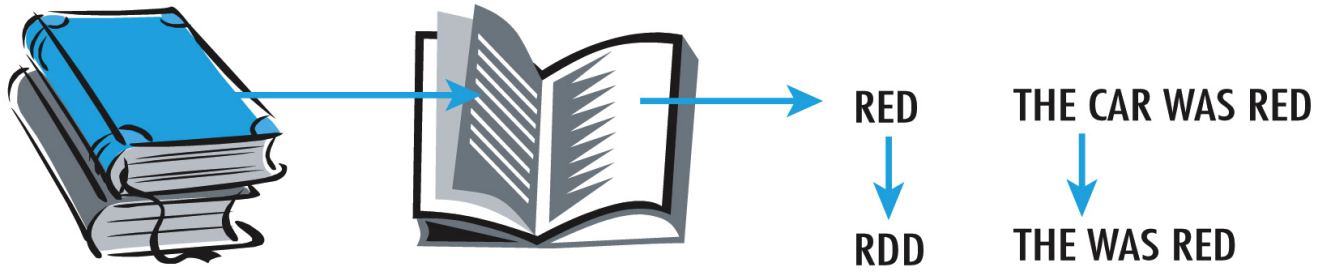


Lopez-Gonazalez Del Rey et al, Front Neuroanat, 2018

Genes

- Units of genetic information that come in pairs
- Located on chromosomes
- 1 chromosome inherited from mother and 1 inherited from father
- 25,000 genes per human genome
- Contain instructions for the production of proteins, which make up the structure of cells and direct their activities

Types of Gene Mutations



Chromosomes are like encyclopedias; one set is from the mother, one is from the father.

Genes are like pages of descriptions.

Mutations are like misspelled words or the disruption of a sentence.

MISSENSE MUTATIONS change one word or letter

THE CAR WAS RED → THE CAR WAS HAT
→ THE CAR WAS RDD

INSERTION MUTATIONS add one word or letter

THE CAR WAS RED → THE CAR HAT WAS RED
→ THE CAR ESW ASR ED

NONSENSE MUTATIONS end the instructions too soon

THE CAR WAS RED → THE CAR

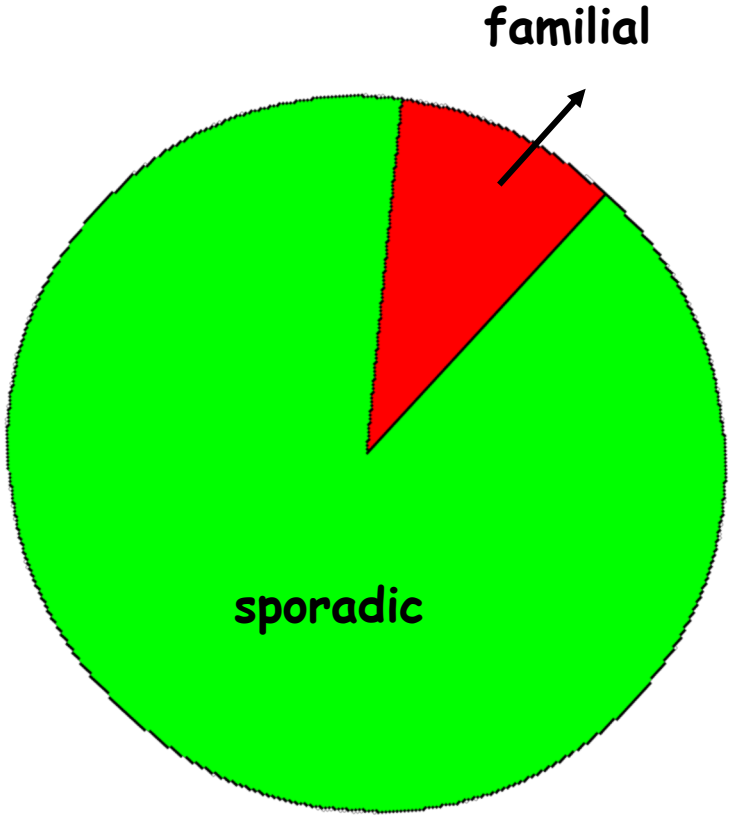
DELETION MUTATIONS

THE CAR WAS RED → THE WAS RED
→ THE RWA SRE D

Greenwood Genetic Center

Sporadic vs Familial PD

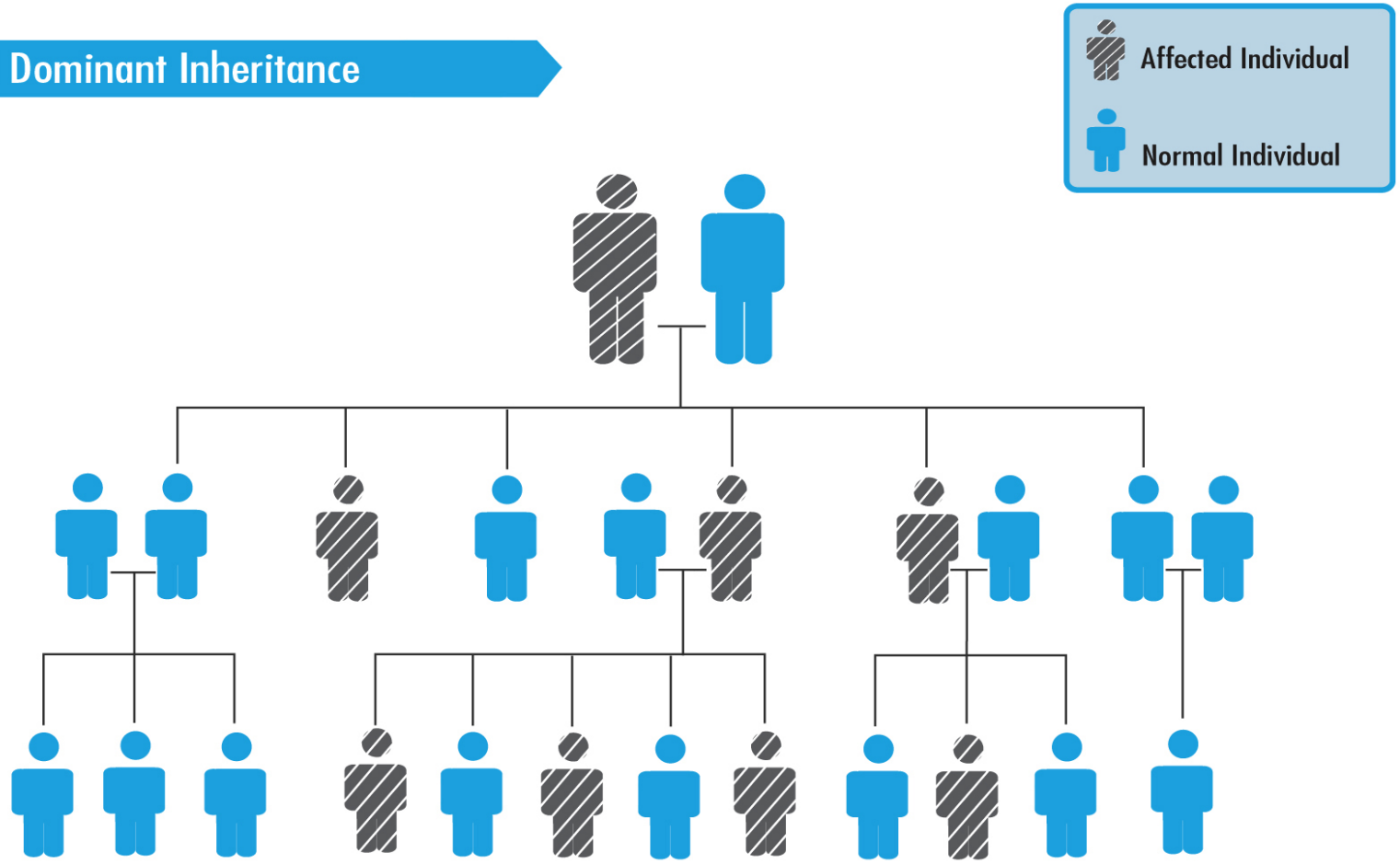
- Idiopathic/Sporadic PD
  - Cause unknown
  - Majority of PD cases
  - Usually no family history
- Familial PD
  - Positive family history
  - Linked to a genetic cause
  - ~10% people with PD



Monogenic PD

- PD caused by a single gene mutation
- Only 1-5% of all PD cases
- Collectively account for about 30% of familial PD
- Modes of inheritance
  - dominant
  - recessive

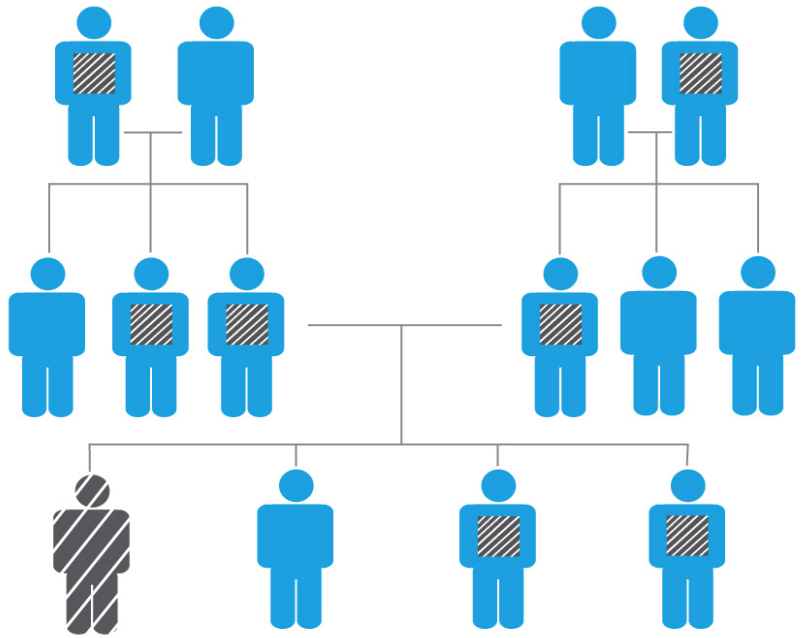
Autosomal Dominant Inheritance



Characteristics of Autosomal Dominant Inheritance

- Multiple generations affected
- Males and females are equally likely to be affected
- Male to male transmission occurs
- Each offspring of an affected parent has a 50% chance of being affected and a 50% chance of being unaffected

Autosomal Recessive Inheritance



Affected Individual

Normal Individual

Carrier

Characteristics of Autosomal Recessive Inheritance

- Greatest recurrence risk is among siblings of affected individuals (horizontal pattern of disease in the family)
- Males and females are equally likely to be affected
- If parents are both carriers of mutations in the same recessive gene, each pregnancy has a 25% chance of inheriting both normal genes, a 50% chance of being a carrier, and a 25% chance of inheriting both gene mutations and being affected
- Ethnic background and consanguinity may influence the likelihood of a specific recessive disease

Age of Onset Terminology

Juvenile onset
(before age 20)

Early onset
(before age 50)

Late onset
(after age 50)

Summary of genes associated with Parkinson's Disease

TABLE 1 | Summary of genes associated with Parkinson's disease.

Locus	Gene	Inheritance	Onset	Location	Variants	Function
PARK1/4	*SNCA*	Dominant Risk factor	EO	4q21.3-q22	5 point mutations, multiplications Rep1 risk variant in the promoter	Synaptic vesicles trafficking
PARK2	*PARKIN*	Recessive	EO	6q25.2-q27	>250 point mutation, ins/de and exon rearrangements	Mitophagy
PARK3	Unknown	Dominant	LO	2p13	?	?
PARK5	*UCHL1*	Dominant	LO	4p13	1 missense variant in one sibling pair	Proteasome
PARK6	*PINK1*	Recessive	EO	1p36.12	>100 point mutations, ins/del and exon rearrangements	Mitophagy
PARK7	*DJ-1*	Recessive	EO	1p36.23	>20 point mutations and deletions	Mitophagy
PARK8	*LRRK2*	Dominant Risk factor	LO	12q12	7 point mutations Risk variants p.R1628P and p.G2385R	Autophagy?
PARK9	*ATP13A2*	Recessive	EO	1p36	>20 point mutations	Lysosomes
PARK10	Unknown	Risk factor	?	1p32	?	?
PARK11	*GIGYF2*	Recessive	EO	2q36-7	7 missense variants	Insulin-like growth factors (IGFs) signaling
PARK12	Unknown	Risk factor	?	Xq21-q22	?	?
PARK13	*HTRA2*	Dominant	?	2p13.1	1 missense variant	Mitophagy,
PARK14	*PLA2G6*	Recessive	EO	22q13.1	>18 missense variants	Lipids metabolism
PARK15	*FBXO7*	Recessive	EO	22q12.3	4 point mutations	Mitophagy
PARK16	Unknown	Risk factor	?	1q32	?	?
PARK17	*VPS35*	Dominant	LO	16q12	2 point mutations	Endosomes
PARK18	*EIF4G1*	Dominant	LO	3q27.1	1 missense variant	Protein translation
PARK19	*DNAJC6*	Recessive	EO	1p31.3	9 missense variants	Endosomes
PARK20	*SYNJ1*	Recessive	EC	21q22.11	3 missense variants	Endosomes
PARK21	*DNAJC13*	Dominant	LO	3q22.1	1 missense variant	Endosomes
PARK22	*CHCHD2*	Dominant	LO/EO	7p11.2	1 missense variant, 1 truncation	Mitochondria-mediated apoptosis and metabolism?
PARK23	*VPS13C*	Recessive	EO	15q22.2	2 missense variants,l truncation	Mitophagy
–	*GBA*	AD, AR in GD Risk factor	LO	lq22	>10 missense variants	Lysosomes
–	*MAPT*	Sporadic Risk factor		17q21.31	H1 haplotype increase PD risk and disease severity	Microtubules

EO, early onset; LO, late onset.

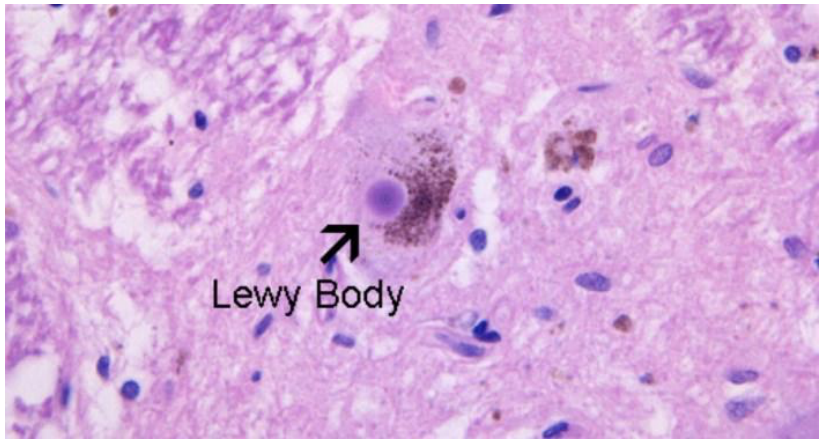
Lopez-Gonazalez Del Rey et al, Front Neuroanat, 2018

PD Causative Genes

- Autosomal Dominant
  - SNCA
  - LRRK2
- Autosomal Recessive
  - Parkin
  - PINK1
  - DJ-1
  - ATP13A2

SNCA mutations

- 1997, researchers at the NIH found mutations in the SNCA gene in several families with a high prevalence of PD (Polymeropoulos et al)
  - Missense mutation A53T in SNCA gene
  - Other pathogenic mutations
- SNCA gene encodes for α-synuclein
  - Function of α-synuclein is not known
  - Abnormal α-synuclein leads to aggregated α-synuclein in Lewy Bodies



Lunati et al, Rev Neurol, 2018

SNCA mutations

- Clinical symptoms and disease course vary depending on specific mutation

P.Ala53Thr	P.Ala30Pro	P.glu46Lys	P.Gly51ASP and p.Ala53Glu
Early-onset	Late-onset	Late-onset	Early onset
dementia	Cerebellar signs	dementia	dementia
Most common			Autonomic dysfunction

Lunati et al, Rev Neurol, 2018

LRRK2 mutations

- Most common genetic cause of PD
  - Mutations found in 5% of all familial and 1-2% of sporadic PD
  - At least 7 pathogenic mutations
  - Variations at the LRRK2 locus also mildly increase the risk for sporadic PD

Michael J. Fox Foundation
Lunati et al, Rev Neurol, 2018
Alessi & Sammler, Science, 2018

LRRK2 mutations

- Clinical significance
  - Late-onset PD
  - Generally good response to dopaminergic therapy
  - Slower progression/less severe clinical symptoms
  - Not everyone who has the gene will develop PD
  - Clinical presentation can vary even within same family

Michael J. Fox Foundation
Lunati et al, Rev Neurol, 2018
Alessi & Sammler, Science, 2018

Selected PD causative genes

SNCA	LRRK2	PRKN	PINK1	DJ-1
Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosomal recessive
Early onset-late onset	Late onset	Early onset	Early onset	Early onset
Rapid progression	Slow progression	Slow progression	Slow progression	Slow progression
Autonomic dysfunction		dystonia	dystonia	dystonia
dementia		Sleep benefit	dementia	dementia
		Preserved smell		

Bruggemann & Klein, GeneReviews, 2013
Schneider & Klein, GeneReviews, 2018
Kasten et al, Mov Disord, 2018

Population differences

- GBA, LRRK2 in Ashkenazi Jews
- LRRK2 in North African Arabs
- MAPT in Caucasians

Ozelius, L Senthil, G et al. NEJM, 2006
Lesage, S Durr, A et al. NEJM, 2006

PD Risk genes

- GBA
- MAPT

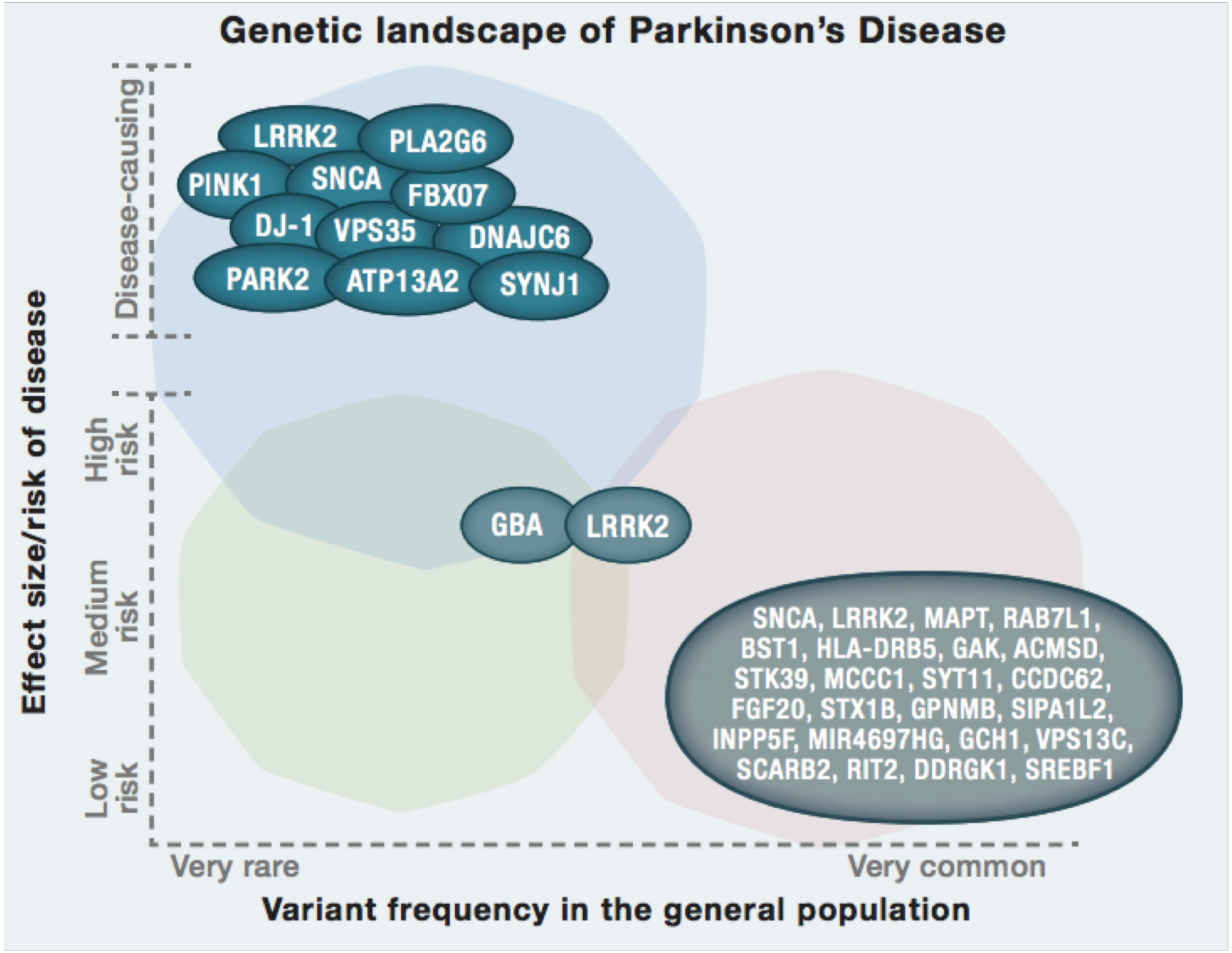
GBA Mutations

- Most common genetic risk factor for PD
- Link to Gaucher Disease (Sidransky et al, 2001)
  - GD patients have 2 copies of mutated GBA gene
  - Unaffected family members frequently exhibited parkinsonism
  - Family members unaffected by GD found to carry a single GBA mutation confer a significant risk for developing PD
  - GBA mutations found 5x as frequently in PD patients vs controls
- Clinical significance in PD
  - Earlier age of onset
  - Dementia

Sidransky et al, N Engl J Med, 2009
O'Regan et al, J Parkinsons Dis, 2017

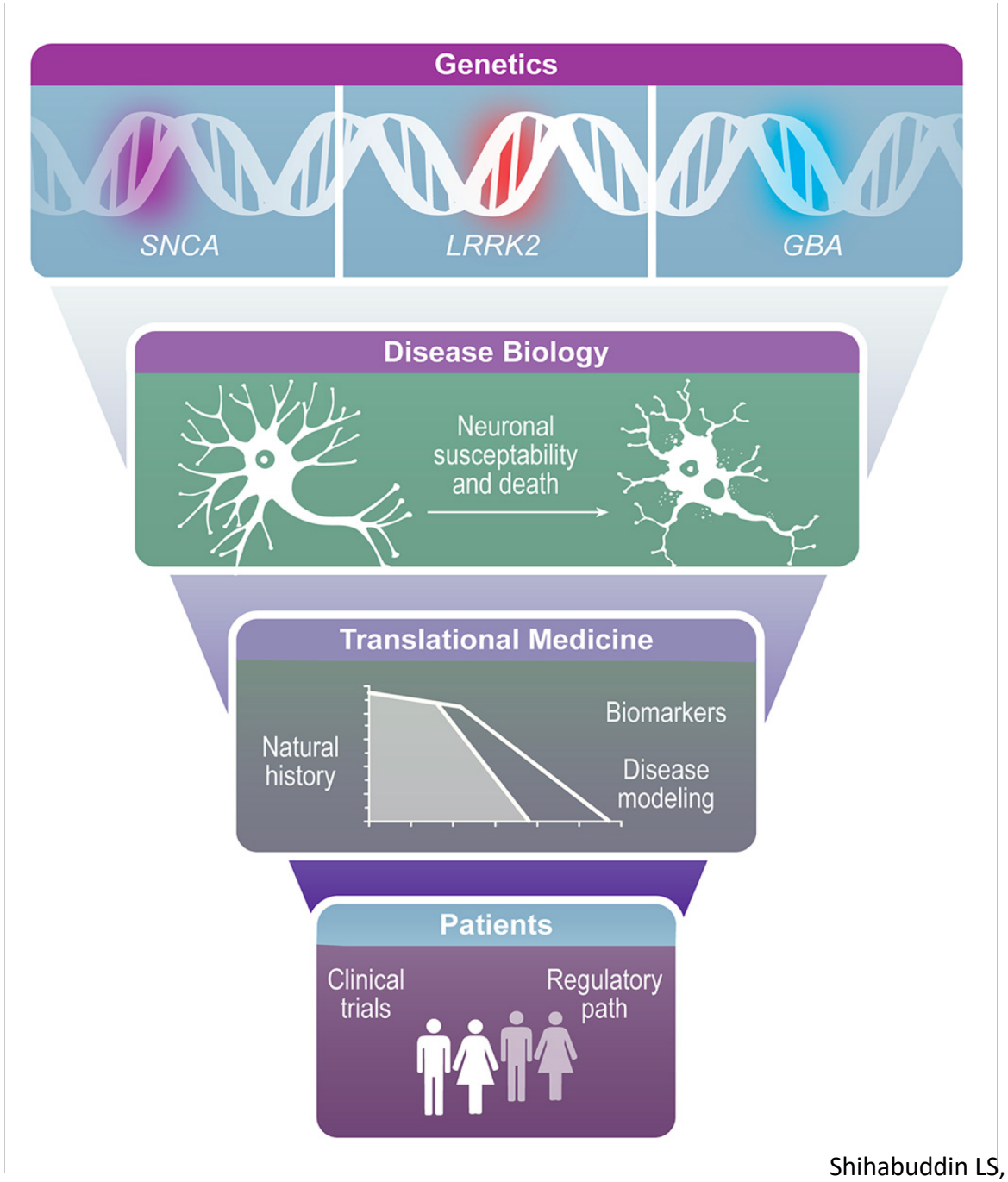
Genetics in sporadic PD

- No large pedigrees (genetic family trees) to search for a genetic contribution to disease
- Genome wide association studies
  - Compare millions of DNA variants (SNPs) between cases and controls
  - Enabled the identification of PD genetic risk loci
  - Most recent GWAS identified 90 PD risk loci



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

Targeted therapies for PD: From genetics to the clinic

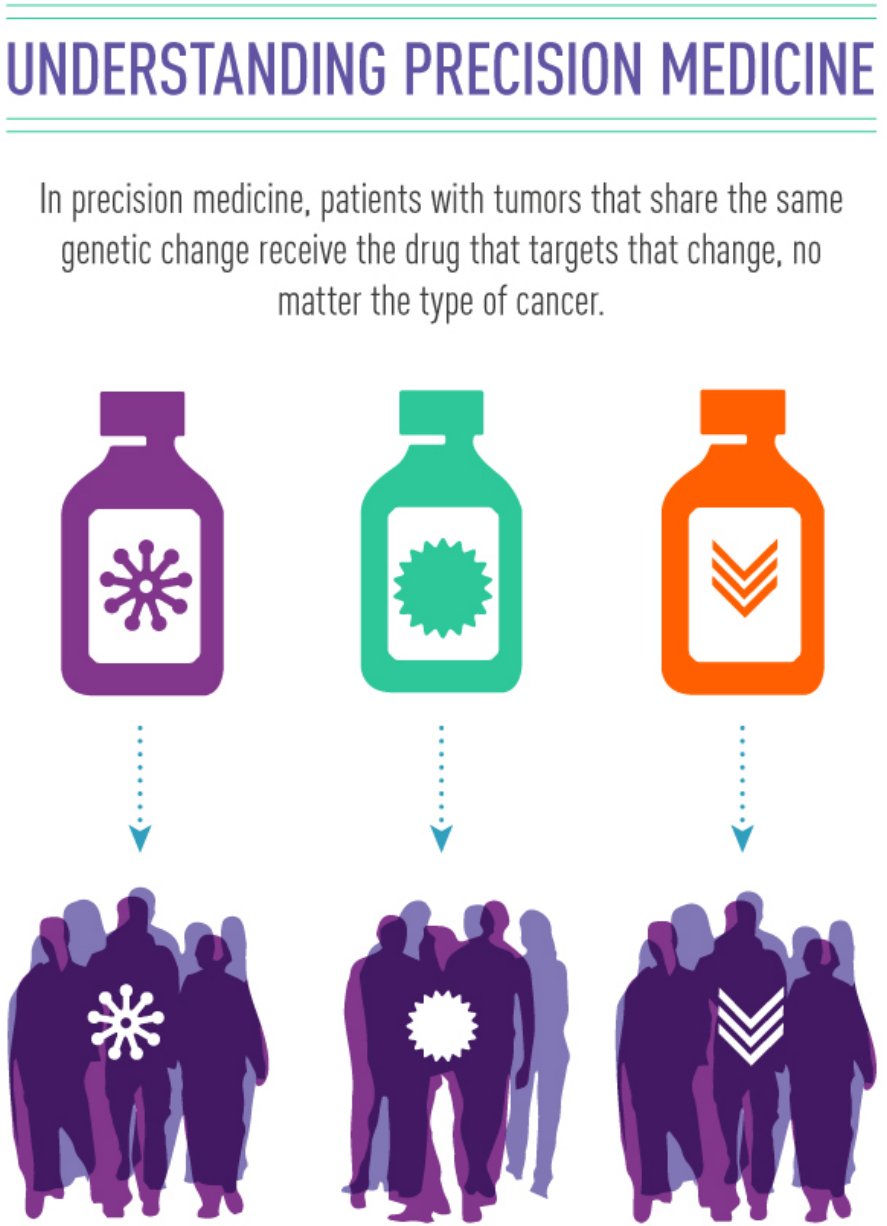


Shihabuddin LS, J Neurosci 2018.

Genetically based therapeutics: Work in progress

- Reduction of α-synuclein
  - Antibodies
  - Vaccines
- Inhibition of LRRK2 activity
- Modulation of GBA related pathways

Future Goals: Precision Medicine



National Cancer Institute

Should I get genetic testing?

Pros	Cons
Support clinical diagnosis	**Does not change treatment (yet!)**
Better understanding of cause/course	**Cost**
Family planning	**Emotional burden**
Involvement in specific clinical trials	**Reveal information about family**
Help advance research	**Secondary findings**
	Results may have uncertain significance
	Testing of limited genetic variants

If I have a mutation, will I get the disease?

Not necessarily	Some people with SNCA or LRRK2 mutations never develop symptoms Risk genes indicate increased risk, but are not causal
Genetic counseling	Highly recommended if considering testing Pre-test counseling: can help understand if testing is right for you Post-test counseling: can help interpret significance of results

Summary

- Genetic factors play a role in both familial and sporadic Parkinson's disease
- Some genetic variants are causative of the disease while others increase the risk
- Genetics gives us clues about impaired pathways and can identify targets for therapeutic interventions
- Genetics can help advance knowledge and treatment of Parkinson's disease, though it is only a piece of the puzzle

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