GENETICS OF PARKINSON'S DISEASE

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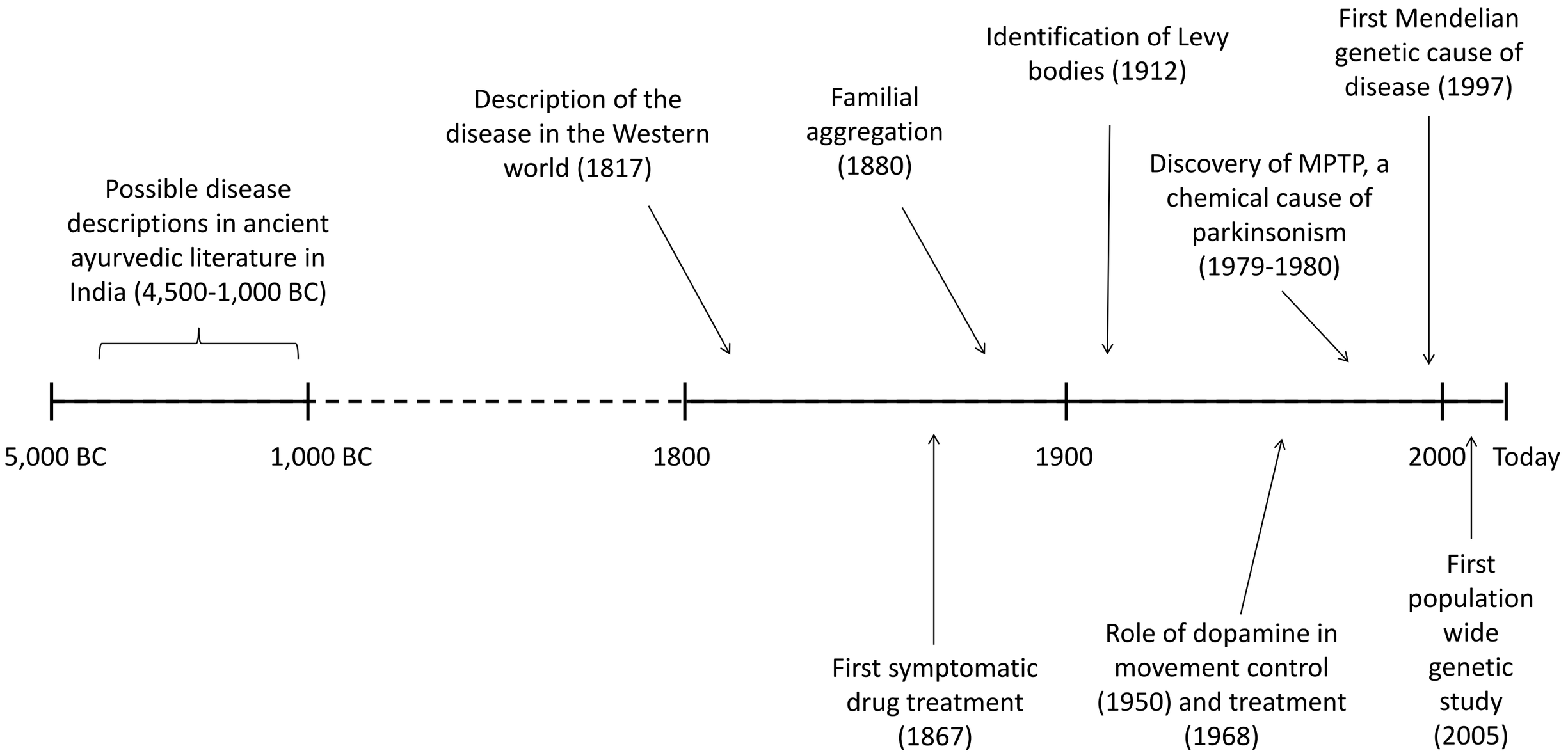
- **Disclosures**
  - No disclosures

PRESENTATION OUTLINE

- History of our knowledge about Parkinson's disease
- Overview of known causes of Parkinson's disease
- Basic genetic concepts
- Known genetic causes of Parkinson's disease
- Genetic risk factors of Parkinson's disease
- Case vignettes

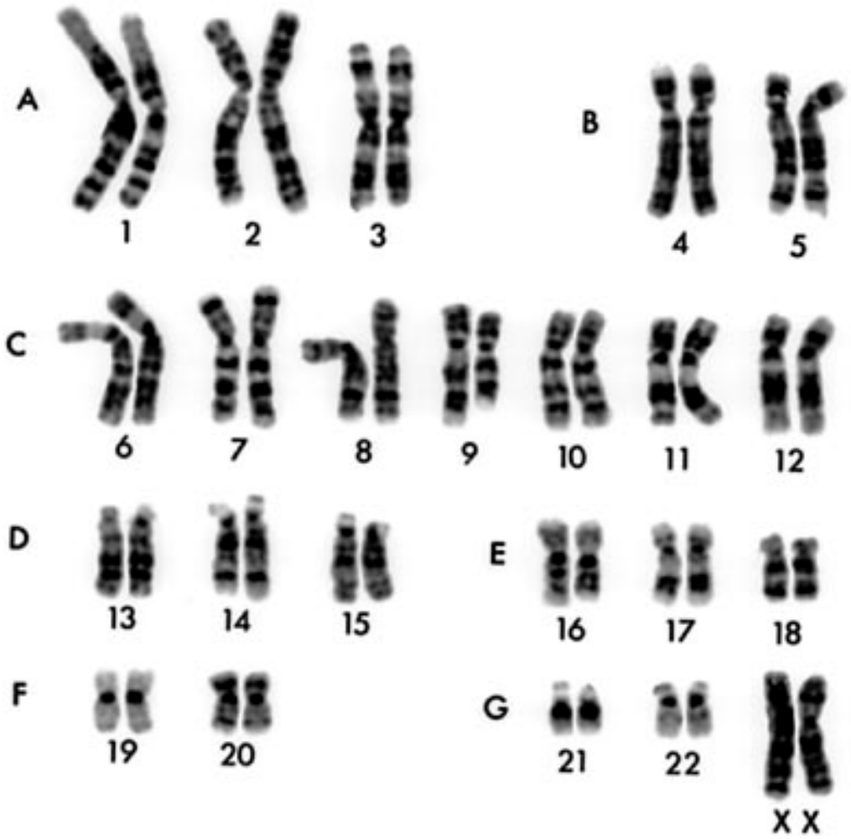
HISTORY OF PARKINSON'S DISEASE KNOWLEDGE



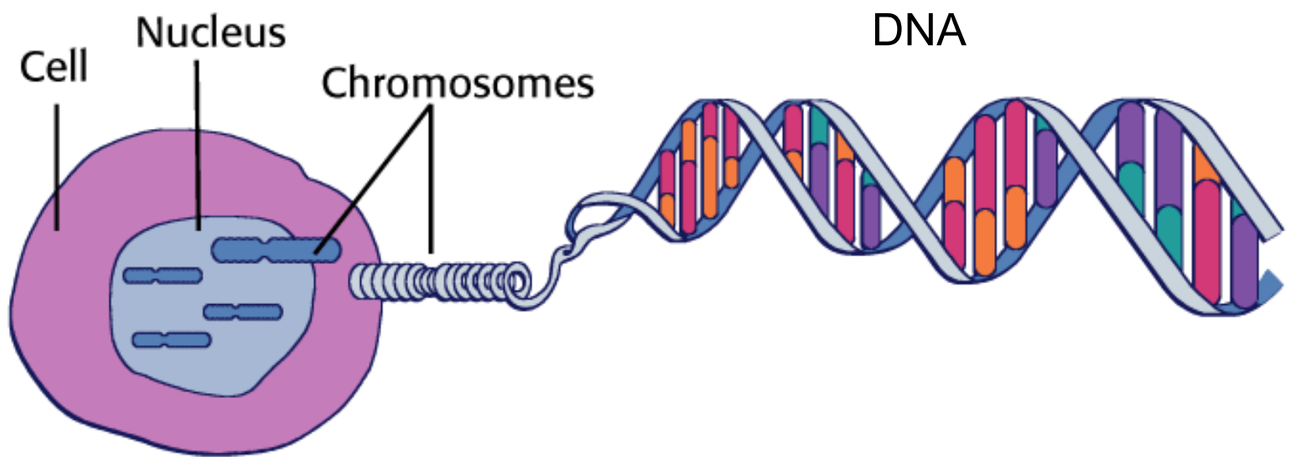
BOTH ENVIRONMENTAL AND GENETIC FACTORS PLAY A ROLE IN PARKINSON'S DISEASE

- Environmental factors
  - Parkinsonism after viral encephalitis
  - Increased risk of PD with exposure to pesticides or herbicides
  - Increased risk of PD with history of head trauma
  - MPTP
- Genetic factors
  - Mutations in a single gene
  - Abnormalities in multiple genes

WE HAVE 23 PAIRS OF CHROMOSOMES INSIDE EACH OF OUR CELLS



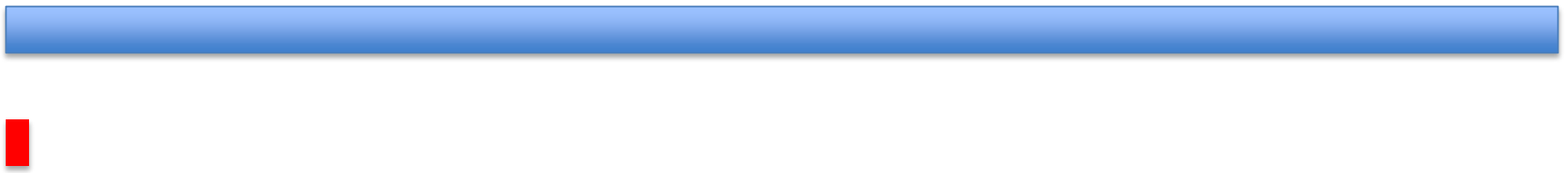
CHROMOSOMES CONTAIN OUR DNA



OUR GENES ARE MADE OF DNA

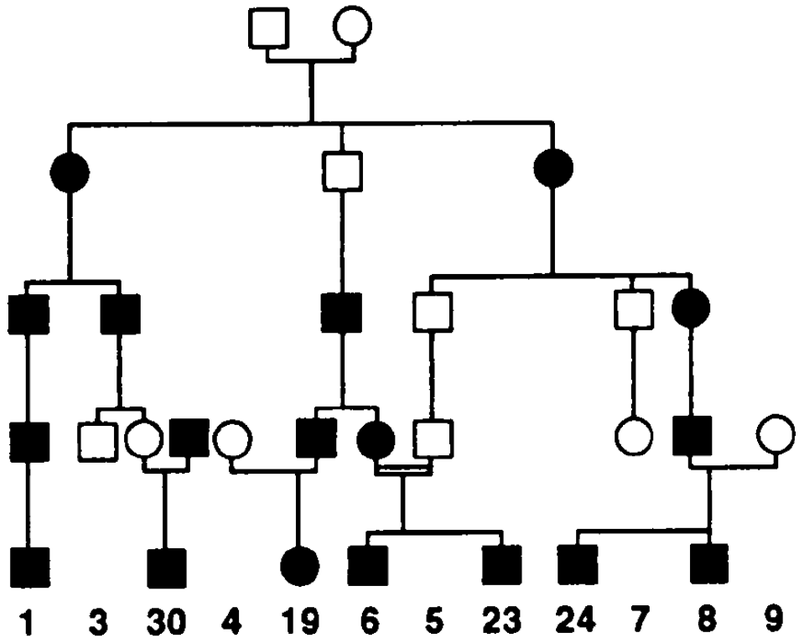
THE HUMAN GENOME BY THE NUMBERS

- Six billion DNA base pairs
- About 20,000 genes
- Our genes correspond to only 1.5% of the total amount of DNA
- The large majority of known genetic diseases are caused by DNA changes in this 1.5% of the genome



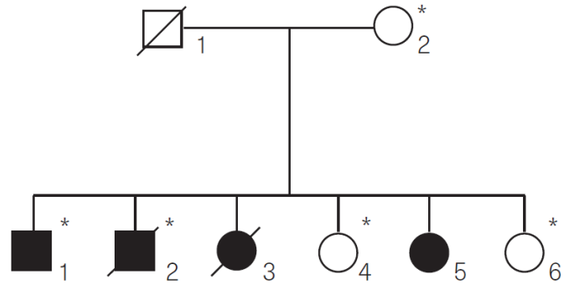
MUTATIONS IN A SINGLE GENE CAN CAUSE PARKINSON'S DISEASE

ALPHA-SYNUCLEIN



Age of onset ~ 45 years

PARKIN



Age of onset ~ 25 years

WE NOW KNOW OF MANY ADDITIONAL SINGLE-GENE OR MONOGENIC CAUSES OF PARKINSON'S DISEASE

Symbol	Gene	Inheritance	Disorder
PARK1	SNCA	AD	EOPD
PARK2	Parkin	AR	EOPD
PARK3	Unknown	AD	Classical PD
PARK4	SNCA	AD	EOPD
PARK5	UCHL1	AD	Classical PD
PARK6	PINK1	AR	EOPD
PARK7	DJ-1	AR	EOPD
PARK8	LRRK2	AD	Classical PD
PARK9	ATP13A2	AR	Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy
PARK10	Unknown	Risk factor	Classical PD
PARK11	Unknown; not GIGYF2	AD	Late-onset PD
PARK12	Unknown	Risk factor	Classical PD
PARK13	HTRA2	AD or risk factor	Classical PD
PARK14	PLA2G6	AR	Early-onset dystonia-parkinsonism
PARK15	FBX07	AR	Early-onset parkinsonian-pyramidal syndrome
PARK16	Unknown	Risk factor	Classical PD
PARK17	VPS35	AD	Classical PD
PARK18	EIF4G1	AD	Classical PD
PARK19	DNAJC6	AR	Juvenille onset, atypical PD
PARK20	SYNJ1	AR	Juvenille onset, atypical PD
PARK21	DNAJC13	AD	Late-onset PD

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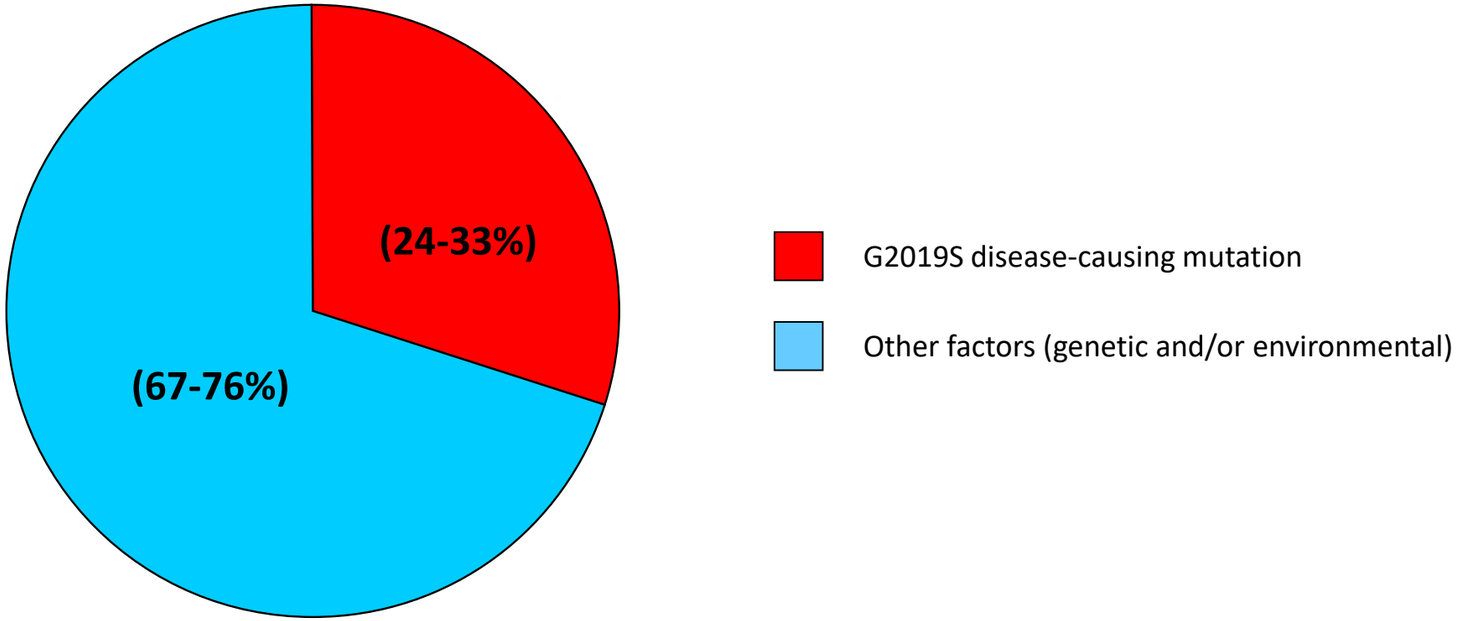
MUTATIONS IN SOME GENES CAUSE A MARKEDLY INCREASED RISK OF PD



Neurochemical Research 32:1700–1708 (2007)

WE ALSO KNOW OF MANY GENES THAT HAVE A SMALL EFFECT ON THE RISK OF PARKINSON'S DISEASE

PD GENE	Odds ratio
Beta acid glucosidase-synaptotagmin XI (GBA-SYT11)	1.82
Inositol polyphosphate-5-phosphatase F (INPP5F)	1.62
Serine threonine kinase 39 (STK39)	1.21
LRRK2	1.15
Bone marrow stromal cell antigen-1 (BST1)	1.13
Signal-induced proliferation-associated 1 like 2 (SIPA1L2)	1.13
RAB29 member RAS oncogene family-nuclear casein kinase and cyclin-dependent kinase substrate 1 (RAB7L1-NUCKS)	1.12
Glycoprotein (transmembrane) nmb (GPNMB)	1.11
Vacuolar protein sorting 13 homolog C (VPS13C)	1.11
DDRGK domain containing 1 (DDRGK1)	1.11
Branched chain ketoacid dehydrogenase kinase-syntaxin 1B (BCKDK-STX1B)	1.10
MicroRNA 4697 (MIR4697)	1.10
Coiled-coil domain containing 62 (CCDC62)	1.10
Sterol regulatory element binding transcription factor 1-retinoic acid induced 1 (SREBF1-RAI1)	0.94
Fibroblast growth factor 20 (FGF20)	0.92
Scavenger receptor class B member 2 (FAM47E-SCARB2)	0.91
GTP cyclohydrolase 1 (GCH1)	0.90
Ras-like without CAAX 2 (RIT2)	0.90
Aminocarboxymuconate semialdehyde decarboxylase-transmembrane protein 163 (ACMSD-TMEM163)	0.87
Methylcrotonoyl-CoA carboxylase 1 (alpha) (MCCC1)	0.84
Major histocompatibility complex, class II, DQ beta 1 (HLA-DQB1)	0.83
Transmembrane protein 175-cyclin G associated kinase-theta diacylglycerol kinase (TMEM175-GAK-DGKQ)	0.79
MAPT	0.77
SNCA	0.76

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PD GENETICS TAKE HOME POINTS

- We know of mutations in about 20 genes that cause PD
- These mutations are rare in most populations, but individuals carrying one of these mutations have a very high risk of developing the disease
- We know of changes in ~10 genes that slightly increase the risk of PD and changes in another ~10 genes that decrease the risk of developing the disease
- These changes are very common in the population, but have very small effects in each of us

CASE VIGNETTES

Is Parkinson's disease caused by exposure to chemicals?

We know of chemicals that increase the risk of developing PD,
but we do not know of chemicals that cause PD

I am the only person in my family with Parkinson's disease, so my disease cannot have a genetic cause.

This is not correct.

In the case of a genetic disease with recessive inheritance, the disease can affect a single member of a family and is not found in the parents.

A new mutation can also arise in a person and cause disease in the absence of family history.

I can learn of my risk of developing PD by sending a sample directly to a company instead of asking my doctor. Is that similar to what the doctor can order?

No, the genetic tests that can be ordered by your doctor are very different from so-called direct-to-consumer genetic testing.

I learned that there are tests that can predict my risk of Parkinson's disease, is that correct?

As a general statement, that is not correct. There are no tests that can accurately predict risk of PD in all individuals. However, if a person carries a known disease-causing mutation, the risk of developing the disease can be estimated.

If I have a Parkinson's disease gene mutation,
will I get the disease?

Not necessarily. Some people have mutations in Parkinson‘s disease genes and never develop the disease.

I heard that genetic tests are very expensive and not covered by insurance. Is that true?

Although some genetic tests are expensive and not always covered by insurance companies, many are not.

I have PD, should I have genetic testing?

The decision is personal, and should be discussed with your family and your doctor, or a qualified genetic counselor. Learning of your PD genetic status does not change your prevention or treatment, but can provide useful information. It is also hoped that increasing our knowledge of PD genetics will help our understanding of the causes of PD and the development of new treatments.

Questions?