Genetics of Parkinson disease

PARKINSON FOUNDATION
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Genetics of Parkinson disease

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  - NIA
  - Univ. of Maryland Strategic Partnership *MPowering the State*

- No conflict of interest.

Outline and Objectives

1. Brief overview of genetics
2. Is Parkinson disease a genetic disease?
3. Should I undergo genetic testing?

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Brief Overview of Genetics –1–

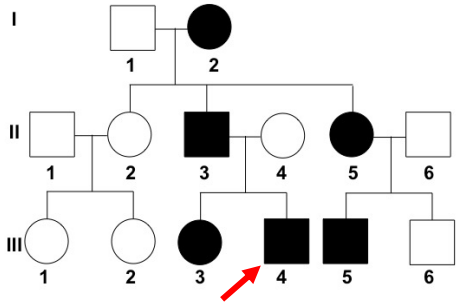
- **Genetics** is the scientific study of how certain *qualities* or *traits* are passed down from one generation to the next, or from parents to offspring.

- **Gregor Mendel** discovered some of the fundamental principals of genetics experimenting with **peas**.
- He coined the terms ***dominant*** and ***recessive***, which we still use today to describe the pattern of an inherited disease within a family.

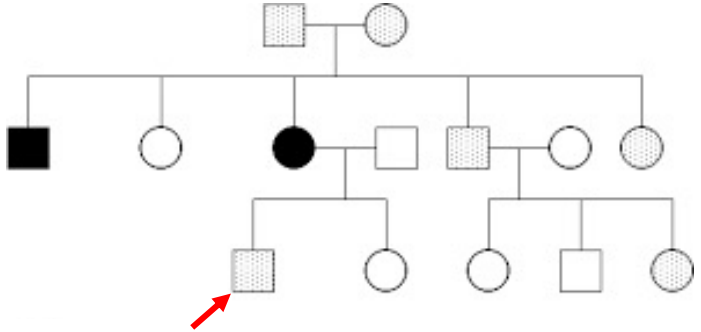
Brief Overview of Genetics -2-

Patterns of "Mendelian inheritance"

Dominant:



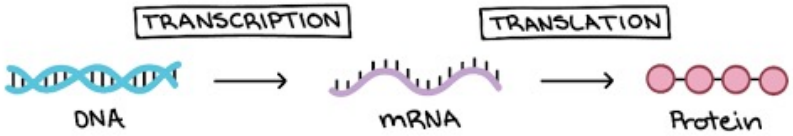
Recessive:



Brief Overview of Genetics -3-

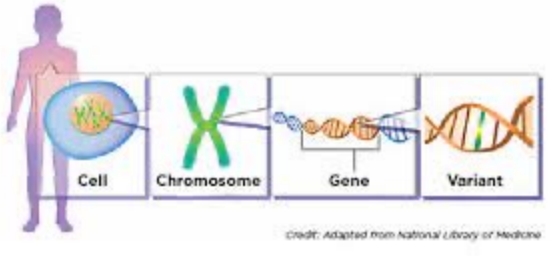
- The information for a single trait that gets passed on from one generation to the next is called a **gene**.
- Today, we know that genetic material is contained in the **DNA** in each cell in our bodies.

- DNA is translated into proteins, the building blocks of our bodies.



Brief Overview of Genetics -4-

- A **gene** is the segment of DNA that contains the code for one specific protein.
- We carry **2 copies of each gene** in each cell of our body: one from our mother and one from our father.
- **Genetic variants** in DNA pop up randomly over time and may affect the *quantity* or *function* of proteins.

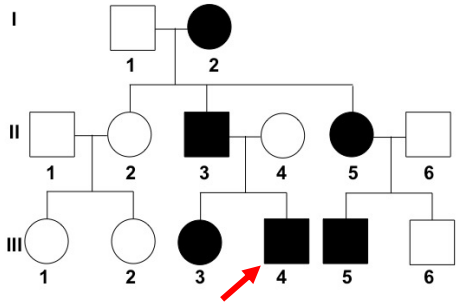


- A **mutation** is a DNA variant in one gene that causes disease.
- Genetic variants/mutations are passed on to the next generation.

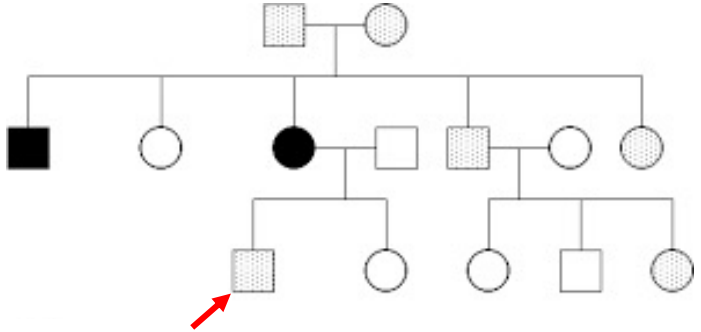
* Brief Overview of Genetics -2-*

***REMEMBER:* Patterns of "Mendelian inheritance"**

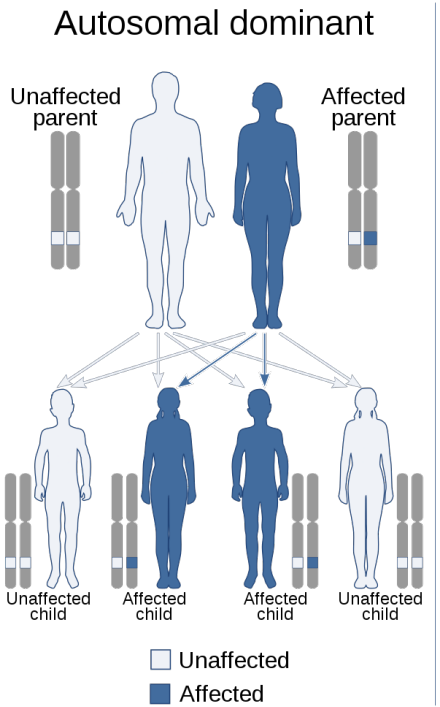
Dominant:



Recessive:



Brief Overview of Genetics -5-



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Does Parkinson disease run in families? -1-

- PD is **fairly common**:
  - almost 1 million people in North America alone
  - an estimated 10 million people worldwide
  - ~1% of the population >60 years of age affected
- However, families with **Mendelian pattern of inheritance** are **exceedingly rare**.
- Therefore, the traditional conclusion was that PD is NOT an inherited disease, and that genetic factors do NOT play an important role in the pathogenesis of PD (or how PD develops).
- HOWEVER…

Does Parkinson disease run in families? -2-

- If you have a 1st degree relative (sibling, parent) with PD, your relative risk of developing PD is more than doubled (2.3x higher) compared to the general population (roughly 2% vs. 1% lifetime risk).
- The risk is not increased for relatives of late-onset PD (age at onset >66 years).
- Twin studies were inconclusive.

Does Parkinson disease run in families? -3-

- The Big Breakthrough of 1997, part 1:

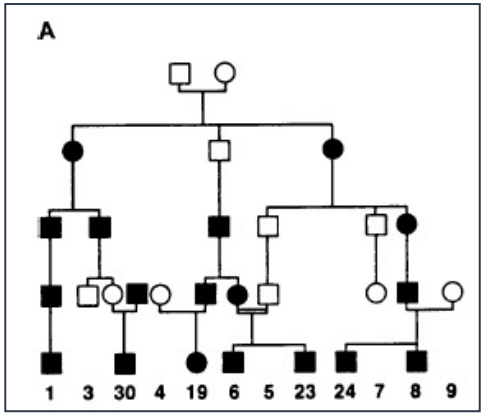
Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease

Mihael H. Polymeropoulos,* Christian Lavedan†, Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra, Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer, Edward S. Stenroos, Settara Chandrasekharappa, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

www.sciencemag.org • SCIENCE • VOL. 276 • 27 JUNE 1997

- An exceedingly **rare form of hereditary PD** with autosomal-**dominant inheritance.**

The *Contursi* kindred:
(Italian-Greek family with autosomal-dominant PD)



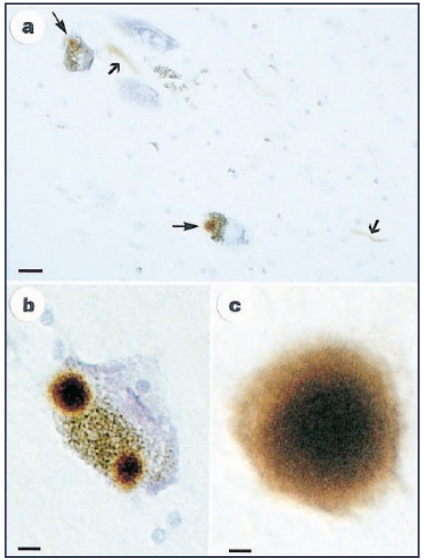
Does Parkinson disease run in families? -4-

- The Big Breakthrough of 1997, part 2:

α-Synuclein in Lewy bodies

Maria Grazia Spillantini
Marie Luise Schmidt
Virginia M.-Y. Lee
John Q. Trojanowski
Ross Jakes
Michel Goedert

NATURE | VOL 388 | 28 AUGUST 1997



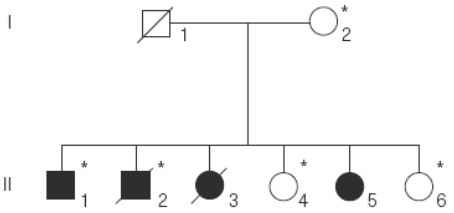
The "normal"/"run-of-the-mill" form of PD has the same protein inclusion bodies ("**Lewy bodies**") as the very rare genetic form of PD, containing **misfolded α-synuclein**.

Does Parkinson disease run in families? -5-

Mutations in the *parkin* gene cause autosomal recessive juvenile parkinsonism

Tohru Kitada*†, Shuichi Asakawa†, Nobutaka Hattori*, Hiroto Matsumine*, Yasuhiro Yamamura‡, Shinsei Minoshima†, Masayuki Yokochi§, Yoshikuni Mizuno* & Nobuyoshi Shimizu†

NATURE | VOL 392 | 9 APRIL 1998



Characteristics of autosomal-recessive juvenile parkinsonism (AR-JP):

- early onset (<40 years)
- foot dystonia at onset
- good response to levodopa therapy
- early onset of levodopa-induced dyskinesia
- slow disease progression
- *pathology:* absence of Lewy bodies

parkin gingerbread

Monogenetic forms of PD –1–

- If a mutation in one gene causes PD and the pattern of inheritance follows one of the classic Mendelian patterns, we call it a *monogenic form of PD*.
- At this point, we know ±12 monogenetic forms of PD.
- Mutations in the genes for α-synuclein and parkin (and most other monogenetic forms of PD) are *very* rare.
- Studying the effects of these mutations has taught us a lot about mechanisms of PD in general.

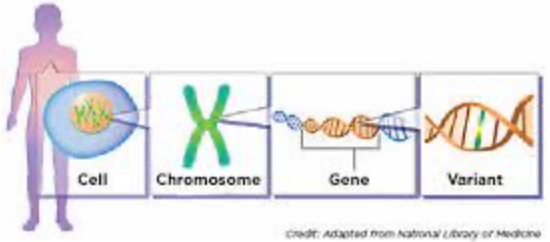
Monogenetic forms of PD –2–

Locus	Locus map	Inheritance pattern	Gene	Clinical features	Reference
PARK1/4	4q22.1	AD	*SNCA*	Early onset, rigidity, cognitive impairment	Polymeropoulos et al. 1997
PARK2	6q26	AR	*PRKN*	Juvenile onset, dystonia	Kitada et al. 1998
PARK6	1p36.12	AR	*PINK1*	Early onset, dystonia	Valente et al. 2002
PARK7	1p36.23	AR	*PARK7*	Early onset, dystonia	Abou-Sleiman et al. 2003
PARK8	12q12	AD	*LRRK2*	Classic PD	Funayama et al. 2002
PARK9	1p36.13	AR	*ATP13A2*	Early onset, cognitive impairment	Di Fonzo et al. 2007
PARK14	22q13.1	AR	*PLA2G6*	Early onset, cognitive impairment, dystonia	Paisán-Ruíz et al. 2009
PARK15	22q12.3	AR	*FBXO7*	Early onset	Di Fonzo et al. 2009
PARK17	16q11.2	Unknown	*VPS35*	Adult onset, cognitive impairment, dystonia	Zimprich et al. 2011
PARK19a/b	1p31.3	AR	*DNAJC6*	Early onset, cognitive impairment	Edvardson et al. 2012
PARK20	21q22.11	AR	*SYNJ1*	Early onset, seizures	Krebs et al. 2013
PARK21	3q22	AD	*DNAJC13*	Classic PD	Vilariño-Güell et al. 2014
PARK23	15q22.2	AR	*VPS13C*	Early onset, rapid progression, cognitive impairment	Lesage et al. 2016

Vázquez-Vélez GE, Zoghbi HY. Parkinson's Disease Genetics and Pathophysiology. Annu Rev Neurosci. 2021 Jul 8;44:87-108.

*What does *genetic* even mean? -4-*

- A **gene** is the segment of DNA that contains the code for one specific protein.
- We carry **2 copies of each gene** in each cell of our body: one from our mother and one from our father.
- **Genetic variants** in DNA pop up randomly over time and may affect the *quantity* or *function* of proteins.



- A **mutation** is a DNA variant in one gene that causes disease.
- Genetic variants/mutations are passed on to the next generation.

Common genetic variants are PD risk factors -1-

- Simple genetic variants of a single base pair in the DNA are common in the human genome.
- Such variants are called *single nucleotide polymorphisms, or SNPs.*
- Some of these variants (or SNPs) have an influence on how likely it is for the person with that variant to develop Parkinson disease.
- The risk of a carrier of such a variant is only *slightly* increased. For example, if the average person without such a variant has a 1% risk for PD, the carrier of such a "PD risk variant" has a 1.2% risk.

Common genetic variants are PD risk factors -2-

Table 1 Results of discovery and replication association analyses

SNP information						Discovery phase (13,728 cases and 95,282 controls)		Replication phase (5,353 cases and 5,551 controls)		Joint phase (19,081 cases and 100,833 controls)	
SNP	Chr.	Position (bp)	Nearest gene(s)	Effect allele	Alternate allele	Effect allele frequency	OR	*P*	OR	*P*	OR	*P*
Genome-wide significant, discovery phase												
rs35749011[a]	1	155,135,036	*GBA-SYT11*	A	G	0.017	1.762	6.09×10^{-23}	2.307	7.48×10^{-9}	1.824	1.37×10^{-29}
rs823118	1	205,723,572	*RAB7L1-NUCKS1*	T	C	0.559	1.126	1.36×10^{-13}	1.109	1.43×10^{-4}	1.122	1.66×10^{-16}
rs10797576	1	232,664,611	*SIPA1L2*	T	C	0.14	1.139	1.19×10^{-8}	1.11	3.38×10^{-3}	1.131	4.87×10^{-10}
rs6430538	2	135,539,967	*ACMSD-TMEM163*	T	C	0.43	0.873	5.56×10^{-15}	0.882	9.42×10^{-6}	0.875	9.13×10^{-20}
rs1474055[a]	2	169,110,394	*STK39*	T	C	0.128	1.213	7.12×10^{-16}	1.218	1.07×10^{-6}	1.214	1.15×10^{-20}
rs115185635[a]	3	87,520,857	*KRT8P25-APOOP2*	C	G	0.035	1.789	2.18×10^{-8}	0.931	0.846	1.142	0.022
rs12637471	3	182,762,437	*MCCC1*	A	G	0.193	0.844	3.32×10^{-16}	0.836	3.72×10^{-7}	0.842	2.14×10^{-21}
rs34311866	4	951,947	*TMEM175-GAK-DGKQ*	T	C	0.809	0.784	3.58×10^{-33}	0.791	6.29×10^{-12}	0.786	1.02×10^{-43}
rs11724635	4	15,737,101	*BST1*	A	C	0.553	1.122	8.07×10^{-13}	1.138	2.73×10^{-6}	1.126	9.44×10^{-18}
rs6812193	4	77,198,986	*FAM47E-SCARB2*	T	C	0.364	0.897	7.17×10^{-11}	0.935	0.011	0.907	2.95×10^{-11}
rs356182	4	90,626,111	*SNCA*	A	G	0.633	0.737	3.23×10^{-67}	0.822	1.75×10^{-12}	0.760	4.16×10^{-73}
rs9275326[a]	6	32,666,660	*HLA-DQB1*	T	C	0.094	0.797	5.82×10^{-13}	0.9	0.018	0.826	1.19×10^{-12}
rs199347	7	23,293,746	*GPNMB*	A	G	0.59	1.123	2.37×10^{-12}	1.072	7.66×10^{-3}	1.110	1.18×10^{-12}
rs117896735[a]	10	121,536,327	*INPP5F*	A	G	0.014	1.767	1.21×10^{-11}	1.404	1.10×10^{-3}	1.624	4.34×10^{-13}
rs3793947[a]	11	83,544,472	*DLG2*	A	G	0.443	0.912	2.59×10^{-8}	0.976	0.201	0.929	3.96×10^{-7}
rs329648	11	133,765,367	*MIR4697*	T	C	0.354	1.1	1.65×10^{-8}	1.121	4.38×10^{-5}	1.105	9.83×10^{-12}
rs76904798	12	40,614,434	*LRRK2*	T	C	0.143	1.17	1.33×10^{-12}	1.11	3.69×10^{-3}	1.155	5.24×10^{-14}
rs11060180	12	123,303,586	*CCDC62*	A	G	0.558	1.101	2.14×10^{-8}	1.114	7.26×10^{-5}	1.105	6.02×10^{-12}
rs11158026	14	55,348,869	*GCH1*	T	C	0.335	0.889	7.13×10^{-11}	0.948	0.039	0.904	5.85×10^{-11}
rs1555399[a]	14	67,984,370	*TMEM229B*	A	T	0.468	0.872	5.53×10^{-16}	0.971	0.144	0.897	6.63×10^{-14}
rs2414739	15	61,994,134	*VPS13C*	A	G	0.734	1.114	4.13×10^{-9}	1.109	7.96×10^{-4}	1.113	1.23×10^{-11}
rs14235	16	31,121,793	*BCKDK-STX1B*	A	G	0.381	1.094	3.89×10^{-8}	1.133	7.72×10^{-6}	1.103	2.43×10^{-12}
rs17649553	17	43,994,648	*MAPT*	T	C	0.226	0.771	4.86×10^{-37}	0.764	7.03×10^{-15}	0.769	2.37×10^{-48}
rs12456492	18	40,673,380	*RIT2*	A	G	0.693	0.905	5.12×10^{-9}	0.9	2.16×10^{-4}	0.904	7.74×10^{-12}
rs62120679[a]	19	2,363,319	*SPPL2B*	T	C	0.314	1.141	2.53×10^{-9}	0.999	0.518	1.097	5.57×10^{-7}
rs8118008[a]	20	3,168,166	*DDRGK1*	A	G	0.657	1.111	2.32×10^{-8}	1.113	1.18×10^{-4}	1.111	3.04×10^{-11}
Previously reported as significant in genome-wide studies												
rs34016896	3	160,992,864	*NMD3*	T	C	0.319	1.08	7.68×10^{-6}	1.028	0.174	1.067	1.08×10^{-5}
rs591323	8	16,697,091	*FGF20*	A	G	0.275	0.921	1.30×10^{-5}	0.902	6.16×10^{-4}	0.916	6.68×10^{-8}
rs60298754	8	89,373,041	*MMP16*	T	C	0.024	1.078	0.181	–	–	1.078	0.181
rs7077361	10	15,561,543	*ITGA8*	T	C	0.874	1.11	3.24×10^{-5}	1.044	0.154	1.092	4.16×10^{-5}
rs11868035	17	17,715,101	*SREBF1-RAI1*	A	G	0.298	0.937	2.17×10^{-4}	0.947	0.036	0.939	5.98×10^{-5}
rs2823357	21	16,914,905	*USP25*	A	G	0.37	1.036	0.032	1.018	0.267	1.031	0.027

Note, only replication-phase *P* values are one-sided. Nearest gene or previously published proximal gene names are included. Chr., chromosome; OR, odds ratio.
[a]Replication genotyping for these SNPs failed assay design or quality control, and a suitable proxy variant was selected (rs35749011, proxy rs71628662; rs1474055, proxy rs1955337; rs115185635, proxy rs62267708; rs117896735, proxy rs118117788; rs3793947, proxy rs12283611; rs1555399, proxy rs1077989; rs62120679, proxy rs10402629; rs8118008, proxy rs55785911).

At this point, >90 such variants have been identified.

These variants explain ~30% of the heritability of PD.

Nalls et al. (2014), Nat Genet

Monogenetic forms of PD -2-

Locus	Locus map	Inheritance pattern	Gene	Clinical features	Reference
PARK1/4	4q22.1	AD	*SNCA*	Early onset, rigidity, cognitive impairment	Polymeropoulos et al. 1997
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Monogenetic forms of PD -3-

- **LRRK2**: autosomal-dominant inheritance.
- Clinical presentation: typical PD.
- Found in 2% of non-familial PD in the U.S.
- Causes up to 40% of *familial PD* in *North African Arabs and Ashkenazi Jews.*
- Incomplete age-dependent *penetrance*:
  - 30% at age 60
  - 50% at age 70
  - 75% at age 80

⇨ LRRK2 mutations are *in between* classic mutations and PD risk factors

Does Parkinson disease run in families? -6-

- **Yes, but** only in *very* few families, due to *exceedingly rare mutations*.
- It is mostly the *risk for PD* that runs in the family.
- Three types of genetic factors:
  - common variants with a very small effect;
  - rare mutations that often, but not always cause disease;
  - exceedingly rare mutations that *always* cause PD.

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Genetic testing for Parkinson disease –1–

PRO:

- Clarify cause of disease.
- Allow participation in studies specific for certain genetic forms of PD.
- *In the future:* gene-specific targeted therapy.
- Family planning

CON:

- No gene-specific therapy yet.
- *Burden of knowledge/ anticipation* for family members.
- Inconclusive results possible.
- Cost. (Insurance coverage?)
- Results difficult to interpret.

Genetic testing for Parkinson disease -2-

Factors that predict a high yield of genetic testing:

- Strong family history.
- Young onset of PD (possibly <50, probably <40).
- Ashkenazi Jewish family or Northern African family origin.

Predictions reg. genetic testing in PD:

Genetic testing will become more and more *common*.

Genetic testing will become more and more *comprehensive*.

- *Whole exome* or *whole genome sequencing*, rather than gene panels.

Genetic testing for Parkinson disease -3-

My suggestions for a pragmatic approach:

- Consider your pros and cons and discuss them with loves ones.
- Talk to a knowledgeable health care provider.
- Consider genetic counseling.
- Testing as part of a genetic study.

Additional resources

- The Michael J Fox Foundation: *www.michaeljfox.org/*
- The Parkinson's Foundation: *www.parkinson.org/*
- Online list of all active clinical trials: *ClinicalTrials.gov*