Genetics of (early onset) Parkinson's disease

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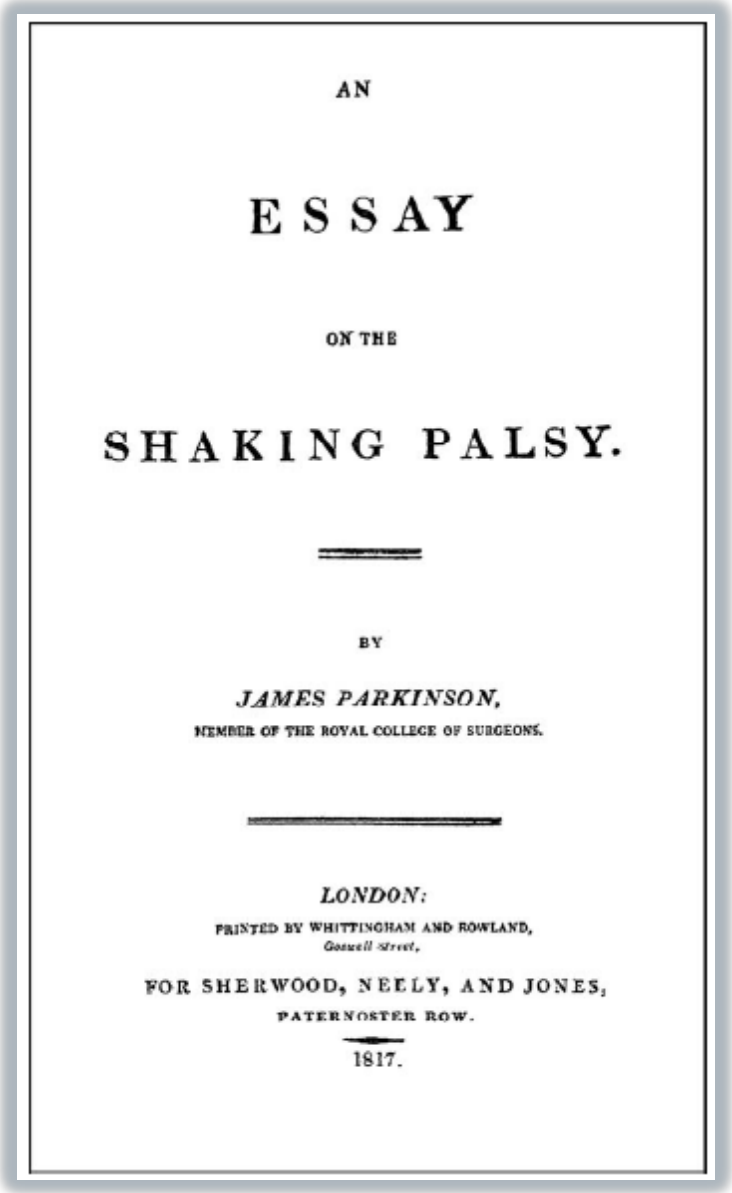
Parkinson disease: a complex phenotype



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

"Involuntary tremulous motion, with lessened muscular power, with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.»

Motor signs

- resting tremor
- bradykinesia
- rigidity
- postural instability

Non motor signs

- Cognitive impairment
- Psychiatric disturbances
- Autonomic dysfunctions

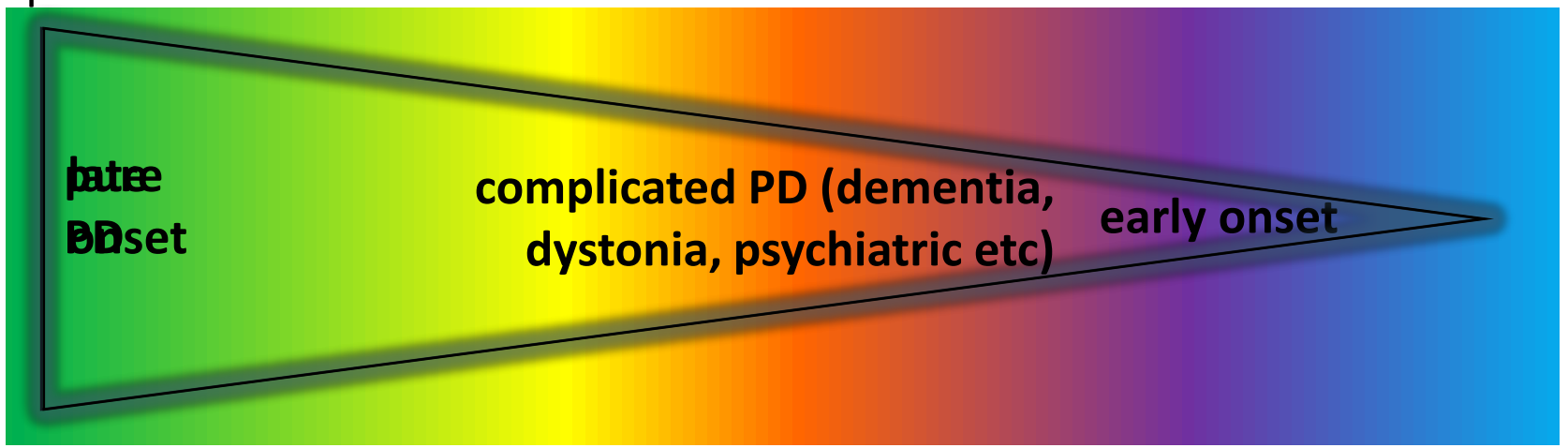
«Plus» signs

- Dementia
- Dystonia
- Spasticity

Genetic factors in PD pathogenesis

polymorphisms
(++ in autosomal dominant
PD genes: RR 1.1-1.4

mutations in autosomal
dominant PD genes: reduced
penetrance (30%): RR 10-20



Heterozygous mutations
in autosomal recessive
PD genes: RR 1.5-2

heterozygous mutations
in other recessive
genes: RR 4-6

mutations in autosomal
recessive PD genes:
full penetrance: 100%

Autosomal recessive early onset «pure» parkinsonisms

Parkin	>>>	PINK1	>	DJ-1
50% fam 10-15% spor		1-8% in different populations		< 1%

Distinct genes, same phenotype

- early onset (<40 years) → DJ1 < Parkin < PINK1
- slow progression
- excellent and sustained response to treatment

Variable phenotypic features, same gene

- dystonia at onset
- sleep benefit, diurnal fluctuations
- hyperreflexia
- treatment-related complications (dyskinesias, behavioral problems)

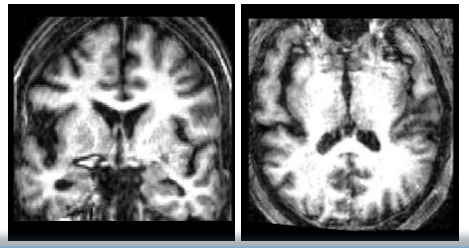
Emerging non motor signs in «pure» AR parkinsonisms

Cognitive impairment

Task (cutoff)	Homozygotes (n = 5)
MMSE (≥24)	28.8 ± 0.6
MoCA (≥26)	21.4 ± 1.3
RAVLT imm (≥28.52)	29.6 ± 3.7
RAVLT del (≥4.69)	6 ± 1.2
Recognition% (>88%)	89.4 ± 7.1
RPM-47 (≤18.96)	23 ± 5.6
Stroop test	−0.6 ± 0.7
Nouns naming (≥28)	27.8 ± 1.4
Verbs naming (≥26)	24.2 ± 2.3
Phonol fluency (≥17.35)	21.6 ± 5.8
Semantic fluency (≥12)	12.8 ± 4.2
Digit span forw (≥7 ± 2)	4.8 ± 0.6
Digit span back (≥5 ± 2)	3.4 ± 0.9

Cognitive decline

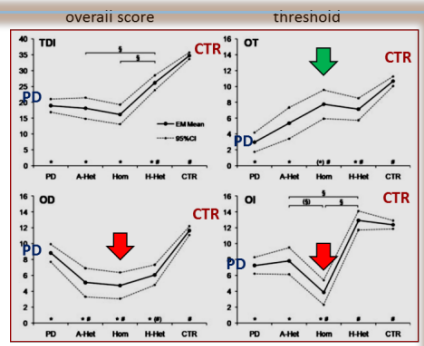
Frontal lobe dysfunction



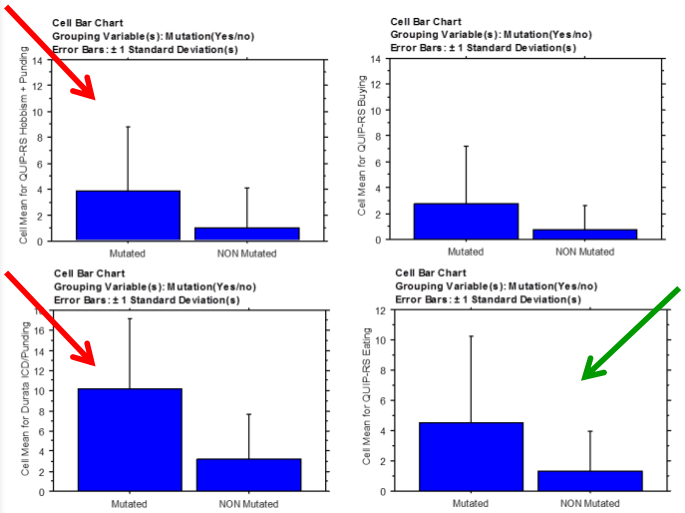
atrophy and cognitive decline

PINK1 olfactory abnormalities

↓↓ odor identification and discrimination



Impulse control behaviour (ICB)



more severe

- binge eating (p= 0.04)
- punding/hobbism (p=0.05)

- ↑ trend for ICB before PD onset (p=0.08)
- stronger family history for ICB (p=0.005)
- longer duration of ICB (p=0.04)

Psychiatric disturbances

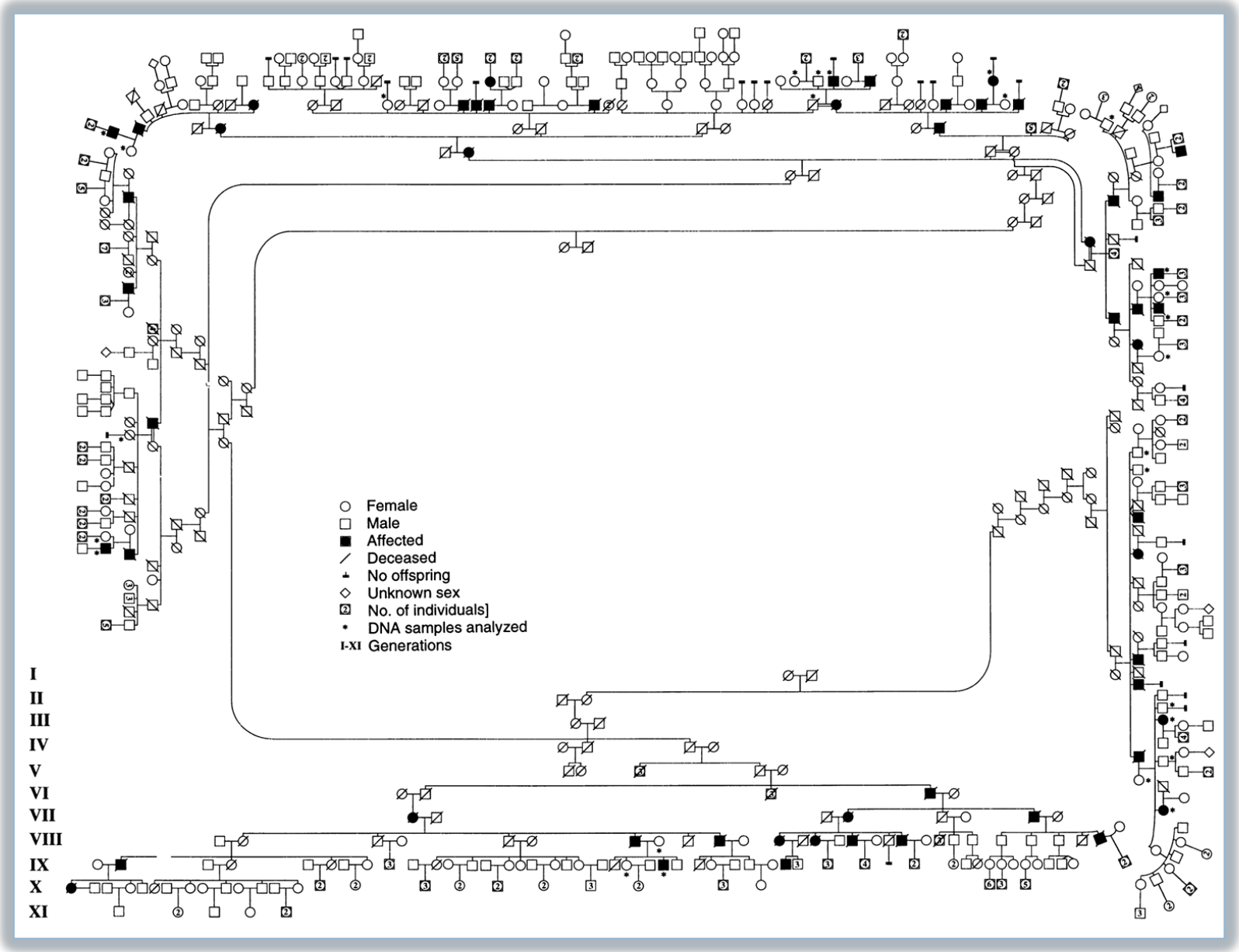
Parkin/ PINK1 → - DOC
- anxiety, depression

PINK1 → - panic disorders
- Schizophr. spectrum

Ricciardi et al , 2014; Sharp et al, 2015

Ferraris et al, 2009; Morgate et al, unpublished data

the Contursi family and the discovery of α-synuclein

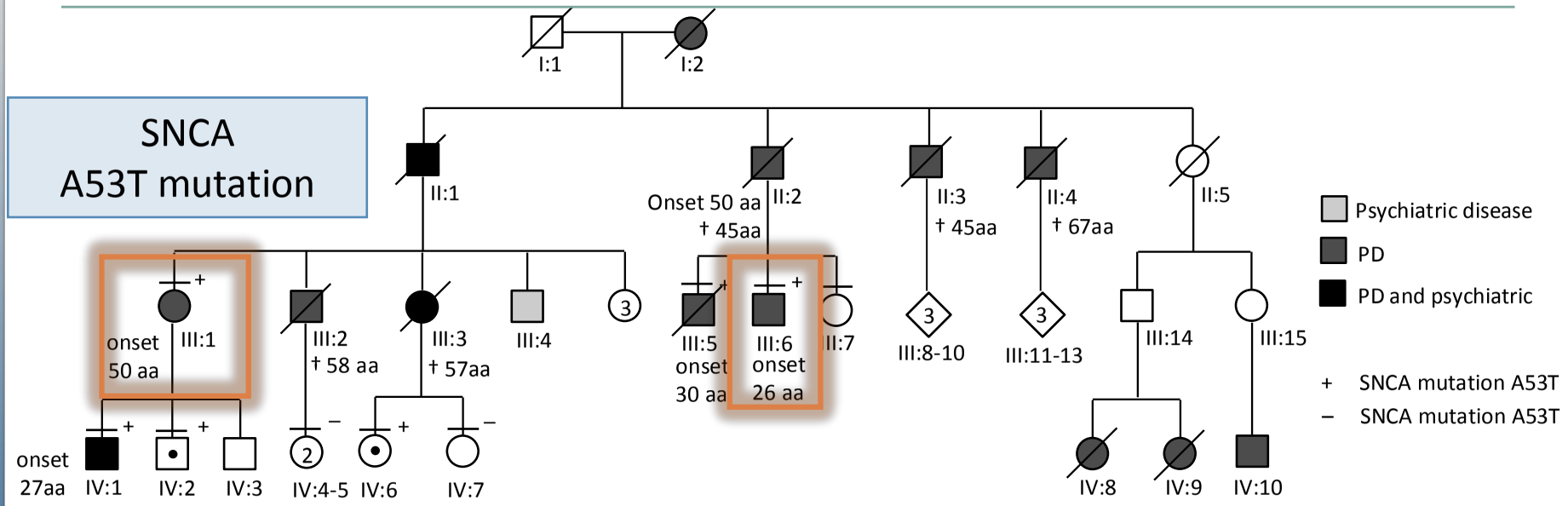


Polimeropoulos et al, Science 1996 and 1997

α-synuclein mutations and PD

Five mutations reported after screening of thousands PD cases

SNCA mutations	p.A53T	p.A30P	p.E46K	p.H50Q	p.G51D
onset	40s	60s	60s	60s	40s
parkinsonism	++, rapid progr.	+	+	+	++, rapid progr.
cognitive impairment	++	+	++	++	-
psychiatric involvement	+	-	+	-	++
autonomic disturbance	+	-	-	-	-/+
L-Dopa response	+	+	+	+	+/-
pyramidal signs	-	-	-	-	++



Courtesy: *M.C. Sensi, A. Fasano, L. Ricciardi*

SNCA gene multiplications and PD phenotypes

Multiplications of the genomic region containing the **SNCA** gene cause α-syn overexpression

correlation between the number of SNCA copies and phenotypic severity

	Three SNCA copies	Four SNCA copies
Subjects	73	27
Asymptomatic carriers	20	0
Age at onset	50 ± 12 (30-77)	37 ± 10 (24-60)
Autonomic dysfunction	41%	100%
Psychiatric disturbances	61%	87%
Cognitive impairment	52%	96%

Elia et al, Mov Disord 2013

PARK8 - LRRK2 - Dardarin

2482 aminoacids, several active domains including a kinase domain

1-2% of sporadic PD ⟵ G2019S mutation ⟶ **5-8% of familial PD**

Founder effect among Ashkenazi Jews and North African Arabs

other mutations are rare (about 10 different mutations reported)

Phenotype of LRRK2 mutations:

- variable presentation, onset 3rd-8th decade
- reduced penetrance: 15-30%, increasing with age
- usually indistinguishable from idiopathic PD

Rare causes of AD PD with similar phenotypes

PARK17 - VPS35

- **p.D620N** mutation detected in ~ 30 cases from 9 families.

DNAJC13

- **p.N855S** mutation detected in PD patients with the same Dutch–German–Russian Mennonite ancestry.

PARK18 - EIF4G1

- Only two mutations found in a few families of different ethnic background:
  - **p.A502V** → very rare
  - **p. R1205H** → detected in patients and controls

Clinical features

- age at onset: 40-80 yrs
- typical PD, relatively mild course, cognition preserved in most cases
- Low penetrance

Vilarino Guell et al , HMG 2013; Struthal et al, JNT 2014; Huttenlocher et al, JMG 2014

Non-canonical PD genes

- ***SCA2*** uninterrupted CAG expansions (usually AD spinocerebellar ataxia)
  - PD with benign course, good response to therapy
  - MRI: no cerebellar atrophy on MRI
  - SPECT: abnormal dopaminergic uptake (similar to PD)

- ***FMR1*** expansions (>200 rpts → intellectual disability in males)
  - Premutations (55-200 rpts): → kinetic tremor, cerebellar gait ataxia, parkinsonism and cognitive decline (FXTAS) in males and females.
  - Gray zone (49-54 rpts) → parkinsonism and idiophatic PD (1-7,5%; 0-11%), ataxia.

- ***C9Orf72*** GGGGCC expansion (>22 rpts, → FTD+ ALS)
  - rare cause of parkinsonism with variable onset (29-64 yrs) and cognitive decline (2/3 patients)
  - family history for atypical parkinsonism with dementia / ALS

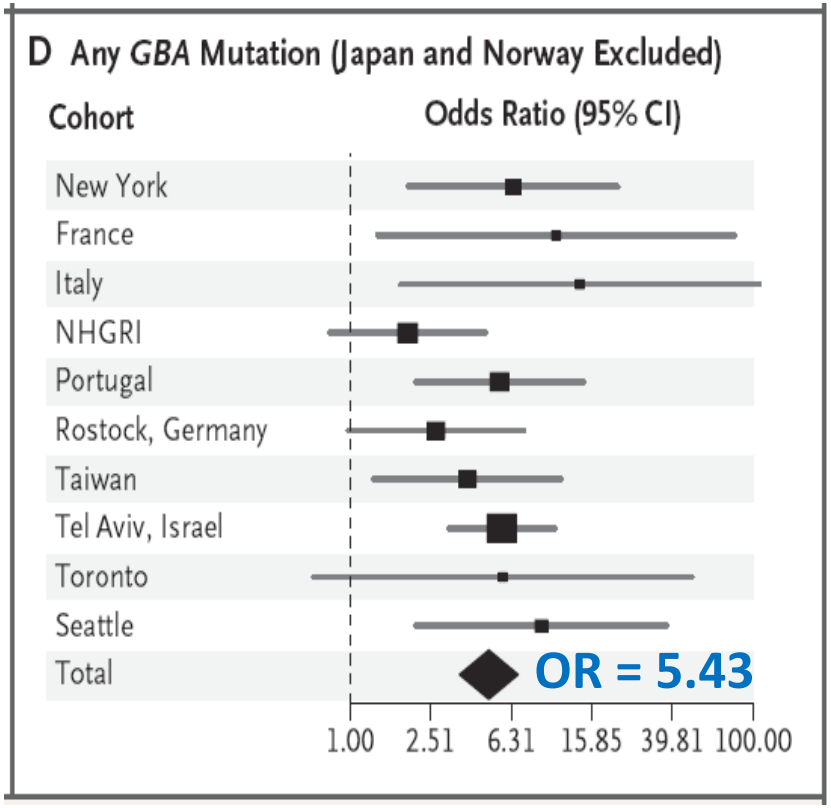
- Other genes of FTD ± parkinsonism:

  MAPT (microtubule-associated protein tau); *PGRN* (progranulin); *TARDBP* (TAR DNA binding protein)

Glucocerebrosidase and PD (++ non-motor signs)

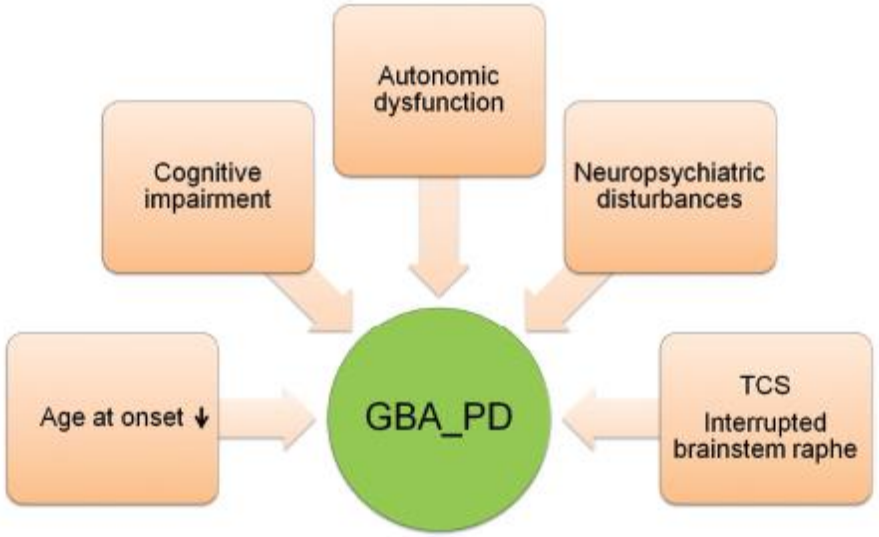
Glucocerebrosidase deficiency → **Gaucher's disease**

heterozygous GBA mutations represent the **most common genetic risk factor for PD** identified to date (4-8% PD vs <1% controls)



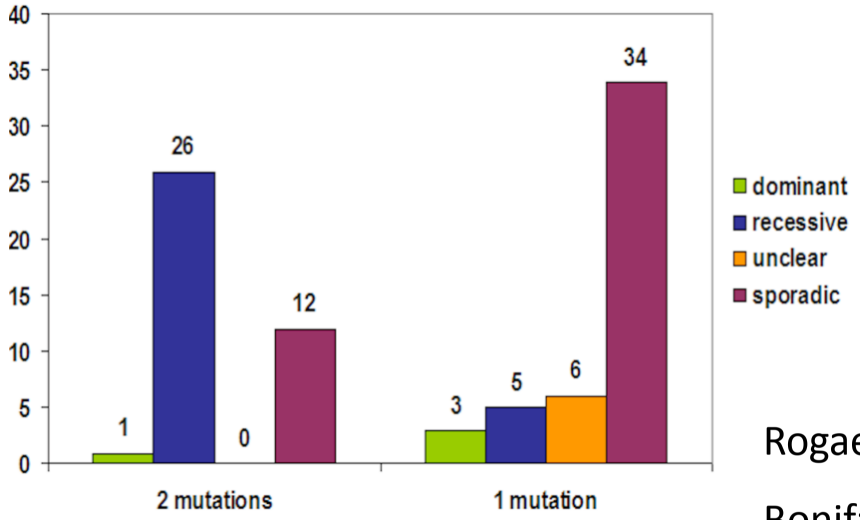
Clinical picture of GB-related PD :

- ++ earlier onset, positive family history
- ++ non-motor features; + severe PD



Sidransky et al, NEJM, 2009; Brockmann et al, Neurology 2011

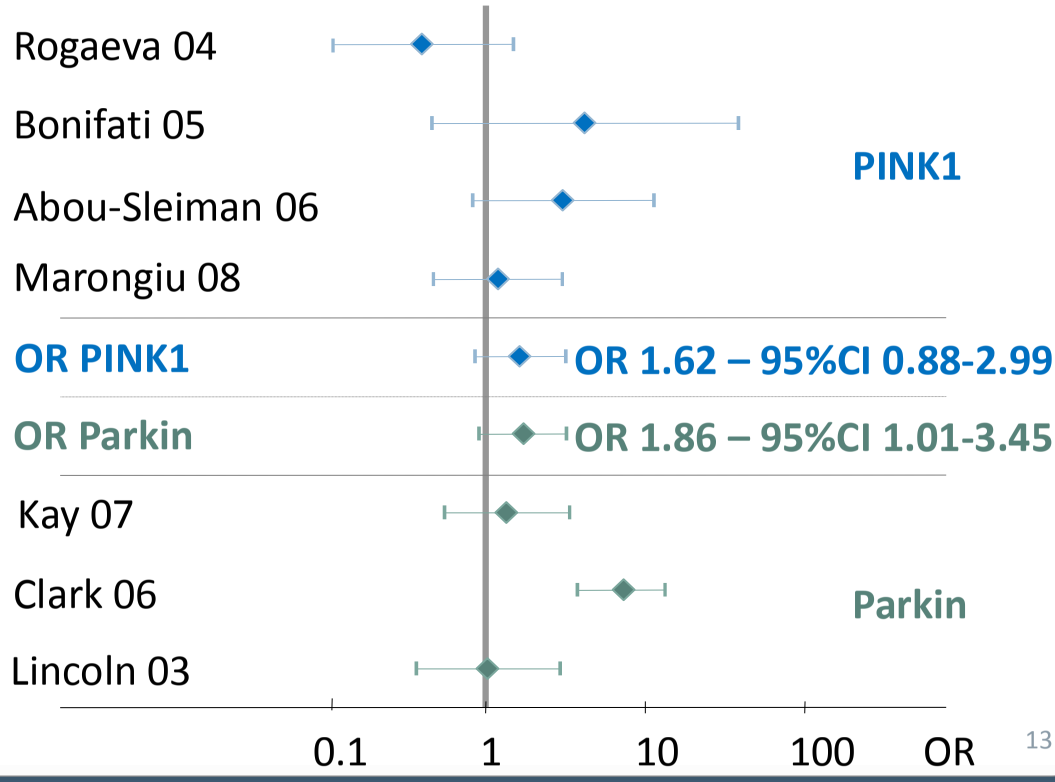
Heterozygous mutations in recessive genes



Heterozygous mutations are more frequent in sporadic cases (heterogeneous phenotypes and higher age at onset).

Also found in healty controls

The risk of developing PD in heterozygous carriers is mildly elevated



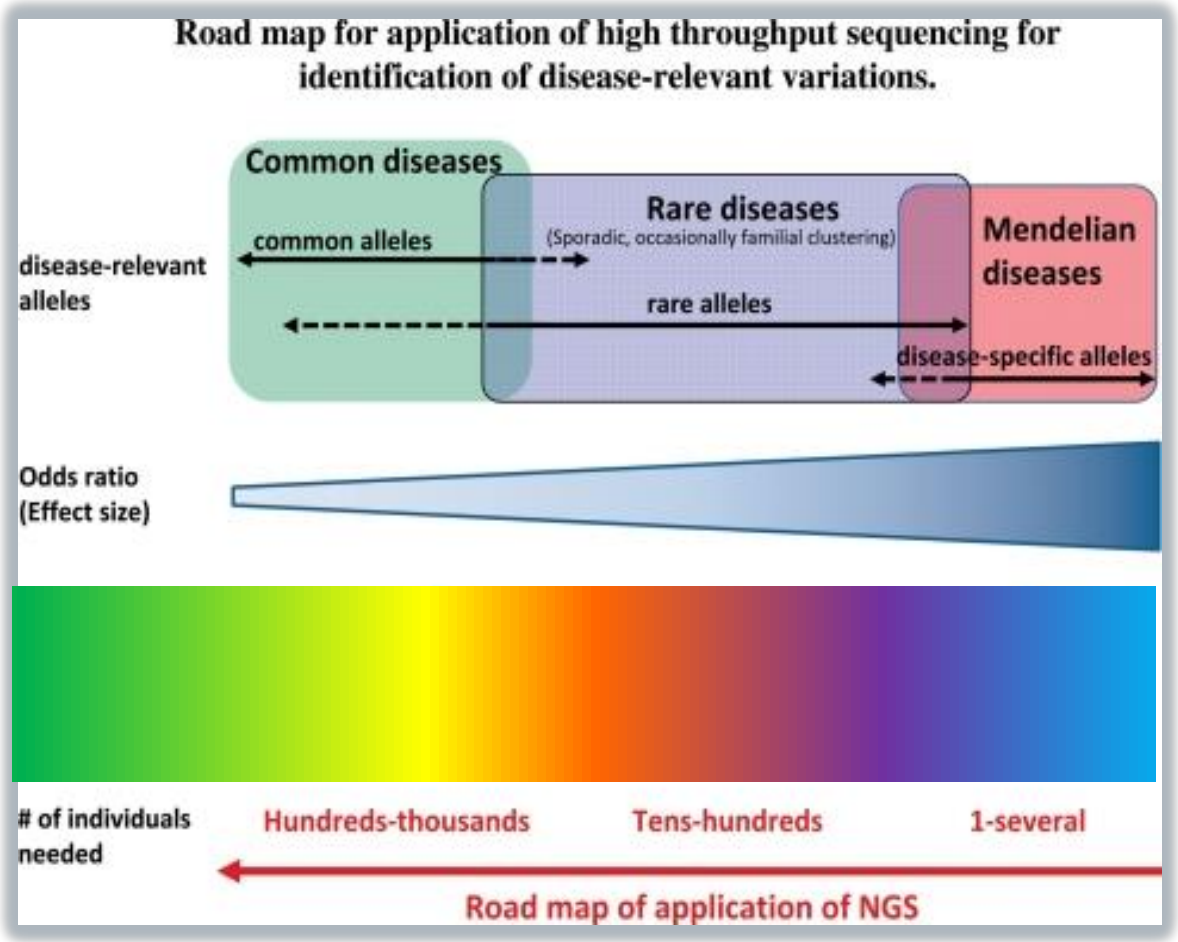
Marongiu et al, Hum Mutat 2008

Association Studies and GWAS in sporadic PD

Chromosome	Gene	Risk variants	Odds ratios (OR)
12q12	**LRRK2(PARK8)**	G2385R, R1628P	2-3[#]
1q22	SYT11	SNPs	1.43[*]
17q21.31	**MAPT**	H1 haplotype	1.4[*]
4p16.3	GAK	SNPs	1.35
4q21-22	**SNCA (PARK1/PARK4)**	Rep1; 5'and 3' UTR variants; SNPs	1.2-1.4
18q12.3	RIT2	SNPs	1.2
2q24.3	STK39	SNPs	1.2
12q24.31	CCDC62/HIP1R	SNPs	1.15
16p11.2	STX1B	SNPs	1.14
4p15	BST1	SNPs	1.1
2q21.3	ACMSD	SNPs	1.02[*]
6p21.32	HLA-DRB5	SNPs	0.95[*]-0.98[#]
others	MCCC1/LAMP3, STBD1, GPNMB, FGF20, ITGA8, PARK16…	SNPs	<1

Polymorphisms, but also rare mutations

Whole exome (and even whole genome) sequencing are likely to replace GWAS to search for genetic modifiers of the phenotype



Tsuji 2010, Hum Mol Genet

PD genetic testing in clinical practice

early onset pure parkinsonism (<40yrs, ++ if consanguinity or AR)	• parkin • PINK1 • (DJ-1)
variable onset, rapidly progressive PD + NMS, (AD inheritance)	• SNCA mut. and mult.
early onset complicated parkinsonism (+ pyramidal, dystonia, dementia; iron dep)	• ATP13A2 • PLA2G6 • (FBXO7)
juvenile onset complicated parkinsonism (+ epilepsy, cognitive impairment)	• SYNJ1 • DNAJC6
Late onset typical PD (≥ 45yrs, AD inheritance)	• LRRK2* • (other AD) • (SNCA dup)

✓ negative genetic tests

✓ Expensive sanger sequencing

NGS-based PD sequencing panels

* : Common mutations

Parkinson gene panels

Target ID	Regions	Coverage	High Coverage (>= 90%)	Low Coverage (< 90%)
ATP13A2	29	100.00 %	29	0
C10ORF2	5	100.00 %	5	0
C19ORF12	3	100.00 %	3	0
COASY	10	100.00 %	10	0
DNAJC6	20	100.00 %	20	0
EIF4G1	33	100.00 %	33	0
FA2H	7	100.00 %	7	0
FBXO7	10	100.00 %	10	0
GBA	11	97.40 %	10	1
LRRK2	52	99.63 %	52	0
MAPT	16	100.00 %	16	0
PANK2	8	100.00 %	8	0
PARK2	16	100.00 %	16	0
PARK7	6	99.71 %	6	0
PINK1	8	100.00 %	8	0
PLA2G6	26	99.84 %	26	0
POLG	22	99.93 %	22	0
SNCA	5	100.00 %	5	0
SYNJ1	34	100.00 %	34	0
VPS35	18	99.71 %	18	0
WDR45	12	100.00 %	12	0

Illumina MiSeq platform

simultaneous sequencing of 21 genes

mean coverage: 99,83%

up to 96 samples in a run

approx. cost x sample: 150-180€