



International Parkinson and
Movement Disorder Society

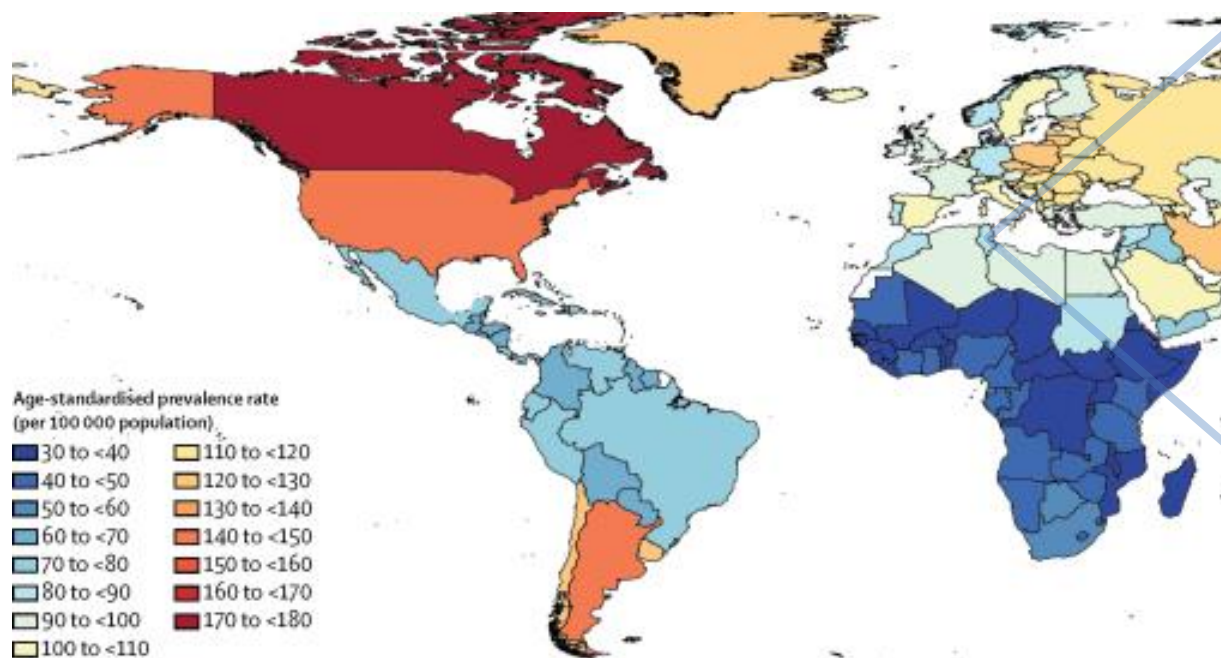
Tunis, Tunisia
December 1-3, 2022

Genetics of Parkinson's disease

Samia Ben Sassi

Mongi Ben Hmida National Institute
of Neurology, Tunis, Tunisia

Parkinson's disease



Second most common neurodegenerative disease after Alzheimer disease.
1-2% of the individuals over age 60 years, worldwide

EOPD : YOPD < 40-50 years / Juvenile PD < 21 years

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
 - muscular rigidity
 - 4–6 Hz rest tremor
 - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

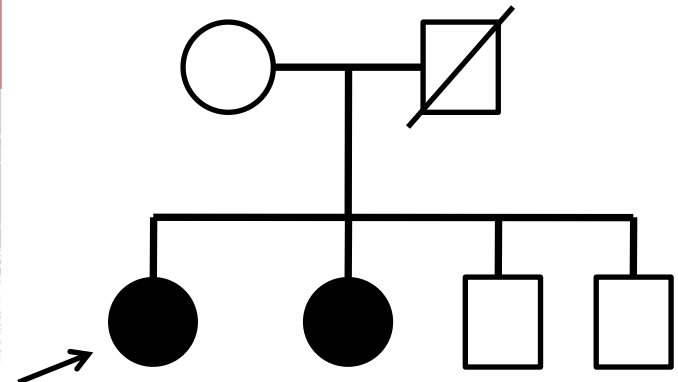
Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- **More than one affected relative**
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

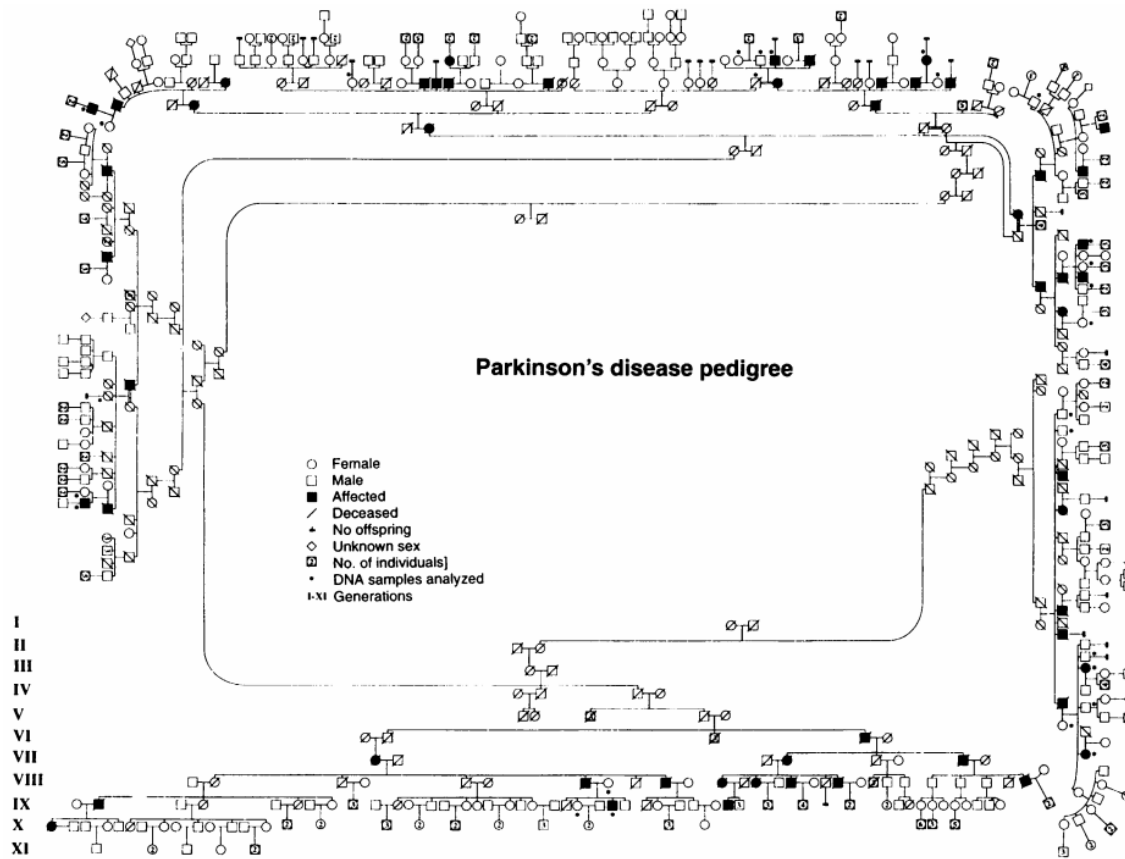
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more



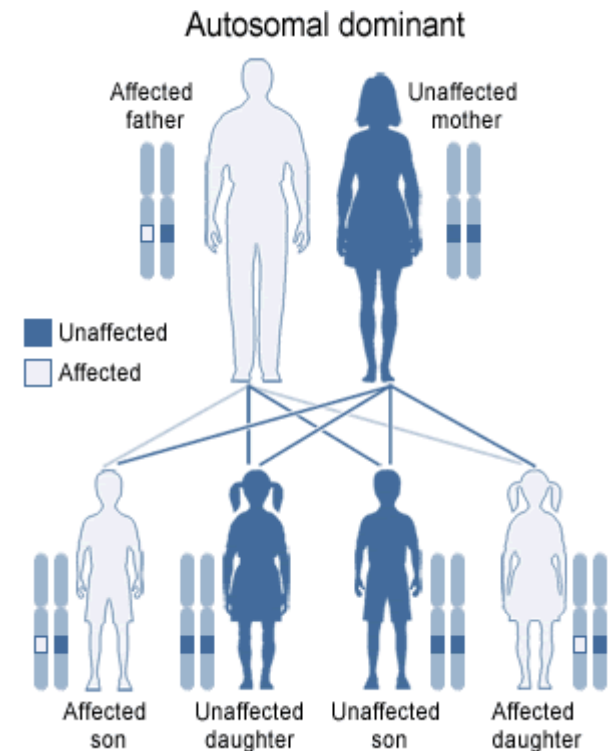
Parkinson's disease
the archetypal “nongenetic”
disorder

Mapping of a Gene for Parkinson's Disease to Chromosome 4q21-q23

Mapping of a Gene for Parkinson's Disease to Chromosome 4q21-q23



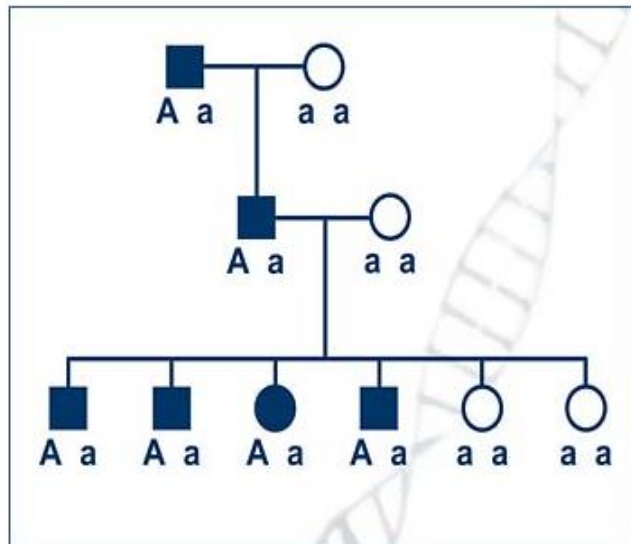
AD early-onset pathologically confirmed PD



U.S. National Library of Medicine

Polymeropoulos et al, 1996

Mapping of a Gene for Parkinson's Disease to Chromosome 4q21-q23 PARK1



Genome scan : 140
genetic markers were
typed in this pedigree at
an average spacing of -20
cM.

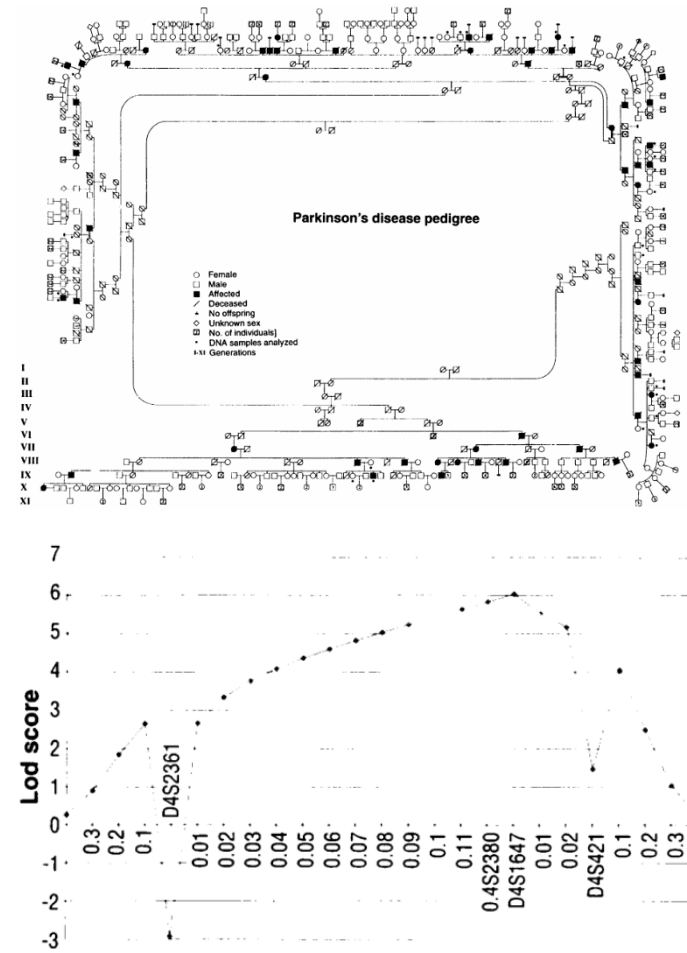


Fig. 2. Multipoint lod score analysis between chromosome 4q markers and the PD locus.

Polymeropoulos et al, 1996

PARK 1

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

- SNCA gene was mapped to the same chromosome region.
- Sequencing the fourth exon of SNCA.

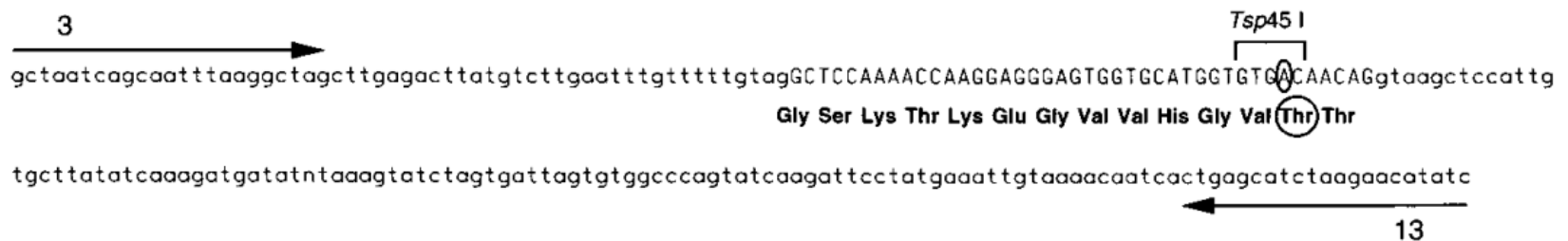
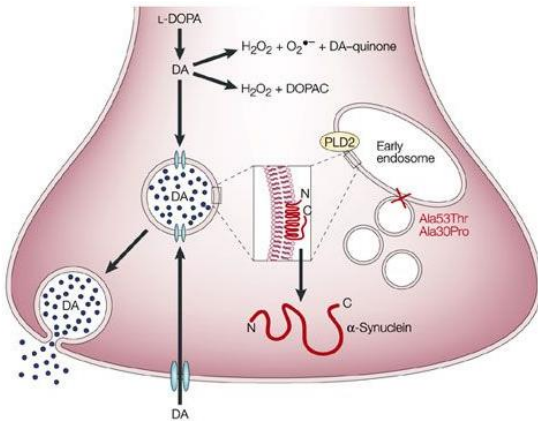


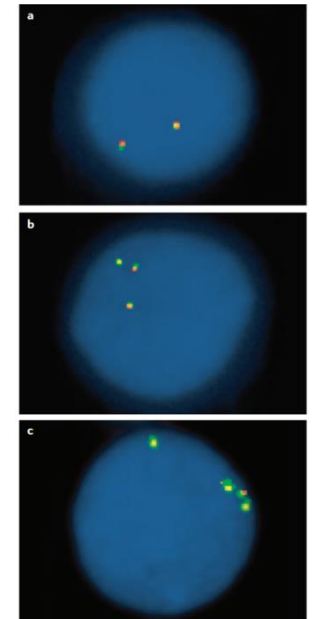
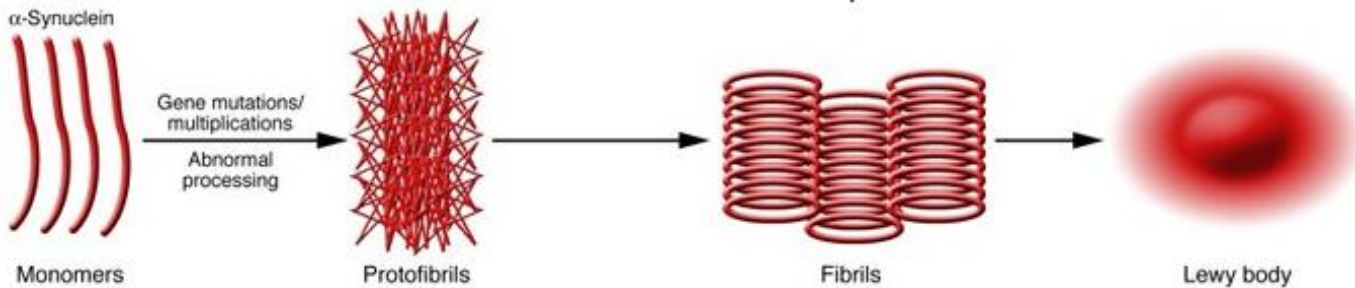
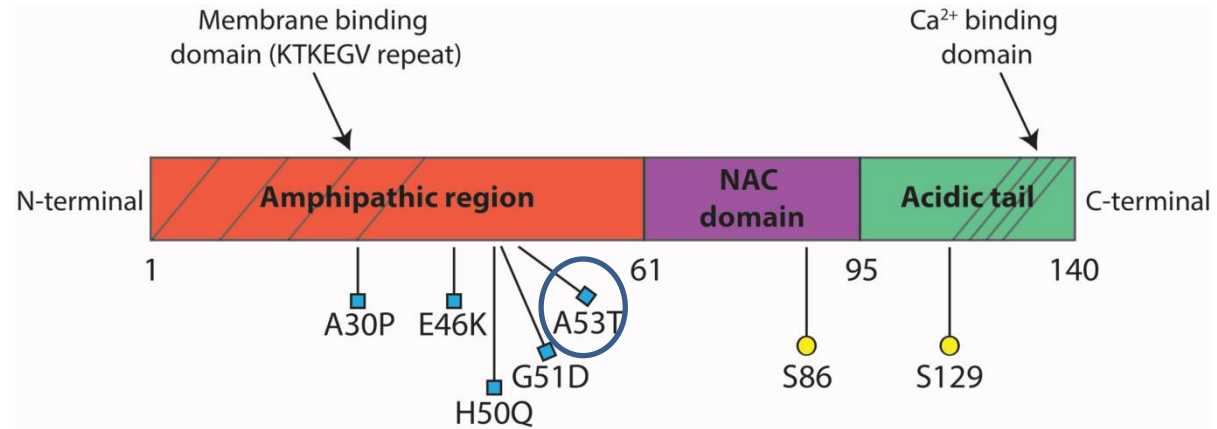
Fig. 1. DNA sequence of the PCR product used for mutation detection.

- A single base pair change at position 209 from G to A (G209A)
→ Ala to Thr substitution at position 53 (Ala53Thr)

α -Synuclein protein



Signal transduction
Membrane vesicle trafficking
Cytoskeletal dynamics.



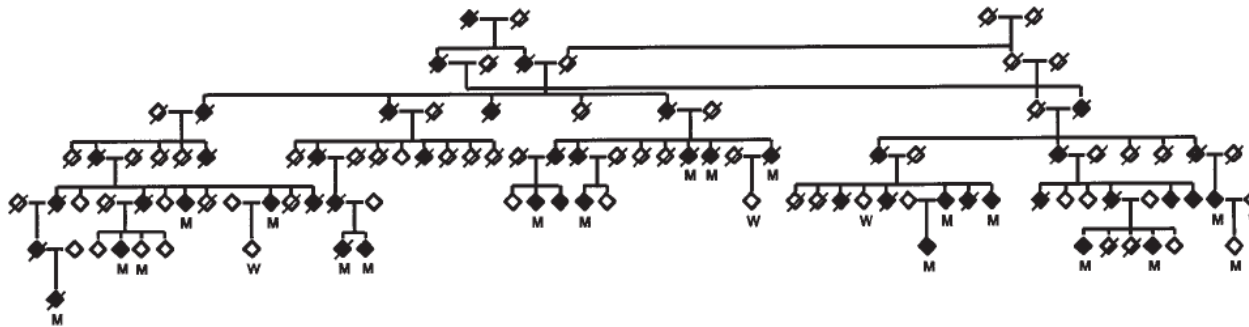
5-10% PD : Monogenetic

Locus (OMIM)	Location	Full Gene Name Approved by HGNC	HGNC Approved Gene Symbol (OMIM)	Inheritance	Disease onset	Lewy bodies
<i>PARK1</i> (168601)	4q22.1	synuclein alpha	<i>SNCA</i> (163890)	AD	Early-onset, late-onset*	C
<i>PARK2</i> (600116)	6q26	parkin RBR E3 ubiquitin protein ligase	<i>PRKN</i> (602544)	AR	Early-onset	NC
<i>PARK3</i> (602404)	2p13		<i>PARK3</i> (Unclear)	AD	Late-onset	NC
<i>PARK4</i> (605543)	4q22.1	synuclein alpha	<i>SNCA</i> (163890)	AD	Early-onset	C
<i>PARK5</i> (613643)	4p13	ubiquitin C-terminal hydrolase L1	<i>UCHL1</i> (191342)	AD	Early-onset, late-onset	NC
<i>PARK6</i> (605909)	1p36	PTEN induced putative kinase 1	<i>PINK1</i> (608309)	AR	Early-onset	NC
<i>PARK7</i> (606324)	1p36.23	parkinsonism associated deglycase	<i>PARK7</i> (602533)	AR	Early-onset	NC
<i>PARK8</i> (607060)	12q12	leucine rich repeat kinase 2	<i>LRRK2</i> (609007)	AD	Late-onset	C
<i>PARK9</i> (606693)	1p36.13	ATPase 13A2	<i>ATP13A2</i> (610513)	AR	Early-onset	NC
<i>PARK10</i> (606852)	1p32		<i>PARK10</i> (Unclear)	Unclear	Late-onset	NC
<i>PARK11</i> (607688)	2q37.1	GRB10 interacting GYF protein 2	<i>GIGYF2</i> (612003)	AD	Late-onset	NC
<i>PARK12</i> (300557)	Xq21-q25		<i>PARK12</i> (Unclear)	X-linked inheritance	Late-onset	NC
<i>PARK13</i> (610297)	2p13.1	HtrA serine peptidase 2	<i>HTRA2</i> (606441)	AD	Late-onset, early-onset*	NC
<i>PARK14</i> (612593)	22q13.1	phospholipase A2 group VI	<i>PLA2G6</i> (603604)	AR	Early-onset	NC
<i>PARK15</i> (260300)	22q12.3	F-box protein 7	<i>FBXO7</i> (605648)	AR	Early-onset	NC
<i>PARK16</i> (613164)	1q32		<i>PARK16</i> (Unclear)	Unclear	Late-onset	NC
<i>PARK17</i> (614203)	16q11.2	VPS35, retromer complex component	<i>VPS35</i> (601501)	AD	Late-onset	NC
<i>PARK18</i> (614251)	3q27.1	eukaryotic translation initiation factor 4 gamma 1	<i>EIF4G1</i> (600495)	AD	Late-onset	NC
<i>PARK19</i> (615528)	1p31.3	DnaJ heat shock protein family (Hsp40) member C6	<i>DNAJC6</i> (608375)	AR	Early-onset	NC
<i>PARK20</i> (615530)	21q22.1	synaptojanin 1	<i>SYNJ1</i> (604297)	AR	Early-onset	NC
<i>PARK21</i> (616361)	20p13	transmembrane protein 230	<i>TMEM230</i> (617019)	AD	Late-onset, early-onset*	C
<i>PARK22</i> (616710)	7p11.2	coiled-coil-helix-coiled-coil-helix domain containing 2	<i>CHCHD2</i> (616244)	AD	Late-onset, early-onset*	NC
<i>PARK23</i> (616840)	15q22.2 11p15.4	vacuolar protein sorting 13 homolog C RIC3 acetylcholine receptor chaperone	<i>VPS13C</i> (608879) <i>RIC3</i> (610509)	AR AD	Early-onset Late-onset, early-onset*	NC NC

Monogenetic PD

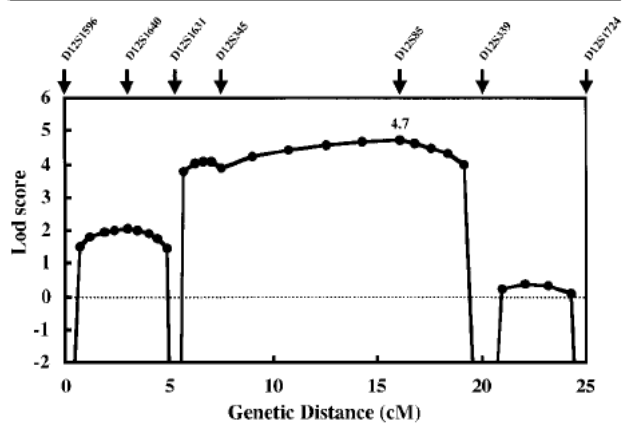
Locus (OMIM)	Location	Full Gene Name Approved by HGNC	HGNC Approved Gene Symbol (OMIM)	Inheritance	Disease onset	Lewy bodies
<i>PARK1</i> (168601)	4q22.1	synuclein alpha	<i>SNCA</i> (163890)	AD	Early-onset, late-onset*	C
<i>PARK2</i> (600116)	6q26	parkin RBR E3 ubiquitin protein ligase	<i>PRKN</i> (602544)	AR	Early-onset	NC
<i>PARK3</i> (602404)	2p13	Parkinson disease 3	<i>PARK3</i> (Unclear)	AD	Late-onset	NC
<i>PARK4</i> (605543)	4q22.1	synuclein alpha	<i>SNCA</i> (163890)	AD	Early-onset	C
<i>PARK5</i> (613643)	4p13	ubiquitin C-terminal hydrolase L1	<i>UCHL1</i> (191342)	AD	Early-onset, late-onset	NC
<i>PARK6</i> (605909)	1p36	PTEN induced putative kinase 1	<i>PINK1</i> (608309)	AR	Early-onset	NC
<i>PARK7</i> (606324)	1p36.23	parkinsonism associated deglycase	<i>PARK7</i> (602533)	AR	Early-onset	NC
<i>PARK8</i> (607060)	12q12	leucine rich repeat kinase 2	<i>LRRK2</i> (609007)	AD	Late-onset	C
<i>PARK9</i> (606693)	1p36.13	ATPase 13A2	<i>ATP13A2</i> (610513)	AR	Early-onset	NC
<i>PARK10</i> (606852)	1p32	Parkinson disease 10	<i>PARK10</i> (Unclear)	Unclear	Late-onset	NC
<i>PARK11</i> (607688)	2q37.1	GRB10 interacting GYF protein 2	<i>GIGYF2</i> (612003)	AD	Late-onset	NC
<i>PARK12</i> (300557)	Xq21-q25	Parkinson disease 12	<i>PARK12</i> (Unclear)	X-linked inheritance	Late-onset	NC
<i>PARK13</i> (610297)	2p13.1	HtrA serine peptidase 2	<i>HTRA2</i> (606441)	AD	Late-onset, early-onset*	NC
<i>PARK14</i> (612593)	22q13.1	phospholipase A2 group VI	<i>PLA2G6</i> (603604)	AR	Early-onset	NC
<i>PARK15</i> (260300)	22q12.3	F-box protein 7	<i>FBXO7</i> (605648)	AR	Early-onset	NC
<i>PARK16</i> (613164)	1q32	Parkinson disease 16	<i>PARK16</i> (Unclear)	Unclear	Late-onset	NC
<i>PARK17</i> (614203)	16q11.2	VPS35, retromer complex component	<i>VPS35</i> (601501)	AD	Late-onset	NC
<i>PARK18</i> (614251)	3q27.1	eukaryotic translation initiation factor 4 gamma 1	<i>EIF4G1</i> (600495)	AD	Late-onset	NC
<i>PARK19</i> (615528)	1p31.3	DnaJ heat shock protein family (Hsp40) member C6	<i>DNAJC6</i> (608375)	AR	Early-onset	NC
<i>PARK20</i> (615530)	21q22.1	synaptojanin 1	<i>SYNJ1</i> (604297)	AR	Early-onset	NC
<i>PARK21</i> (616361)	20p13	transmembrane protein 230	<i>TMEM230</i> (617019)	AD	Late-onset, early-onset*	C
<i>PARK22</i> (616710)	7p11.2	coiled-coil-helix-coiled-coil-helix domain containing 2	<i>CHCHD2</i> (616244)	AD	Late-onset, early-onset*	NC
<i>PARK23</i> (616840)	15q22.2	vacuolar protein sorting 13 homolog C	<i>VPS13C</i> (608879)	AR	Early-onset	NC
	11p15.4	RIC3 acetylcholine receptor chaperone	<i>RIC3</i> (610509)	AD	Late-onset, early-onset*	NC

A New Locus for Parkinson's Disease (*PARK8*) Maps to Chromosome 12p11.2–q13.1



Pedigree of the Sagamihara family

Parametric multipoint linkage analysis.



Nonparametric multipoint linkage analysis.

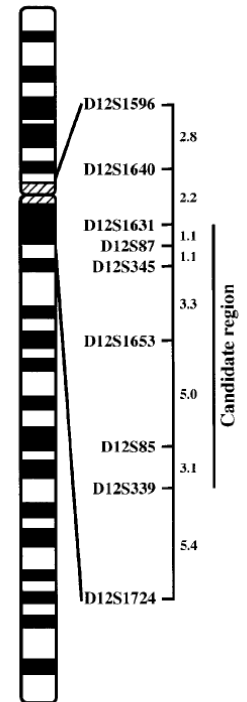
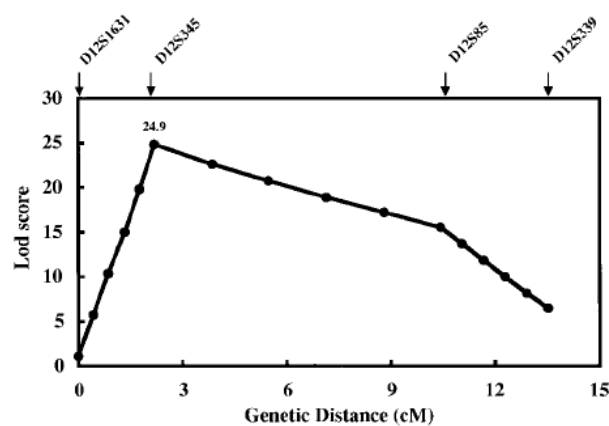


Fig 1. Microsatellites of chromosome 12 used in this study. The bold bar indicates the 13.6cM interval of the candidate region for the new parkinsonism locus.

Cloning of the Gene Containing Mutations that Cause *PARK8*-Linked Parkinson's Disease

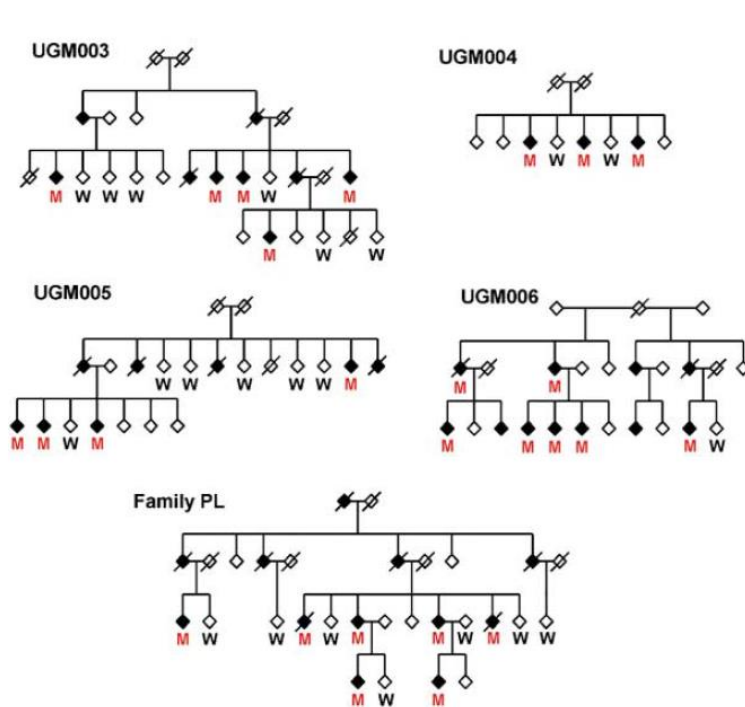


Figure 3. *PARK8*-Linked Pedigrees

UGM003, UGM004, UGM005, and UGM006 originate from the Basque region; kindred PL was collected in the United Kingdom.

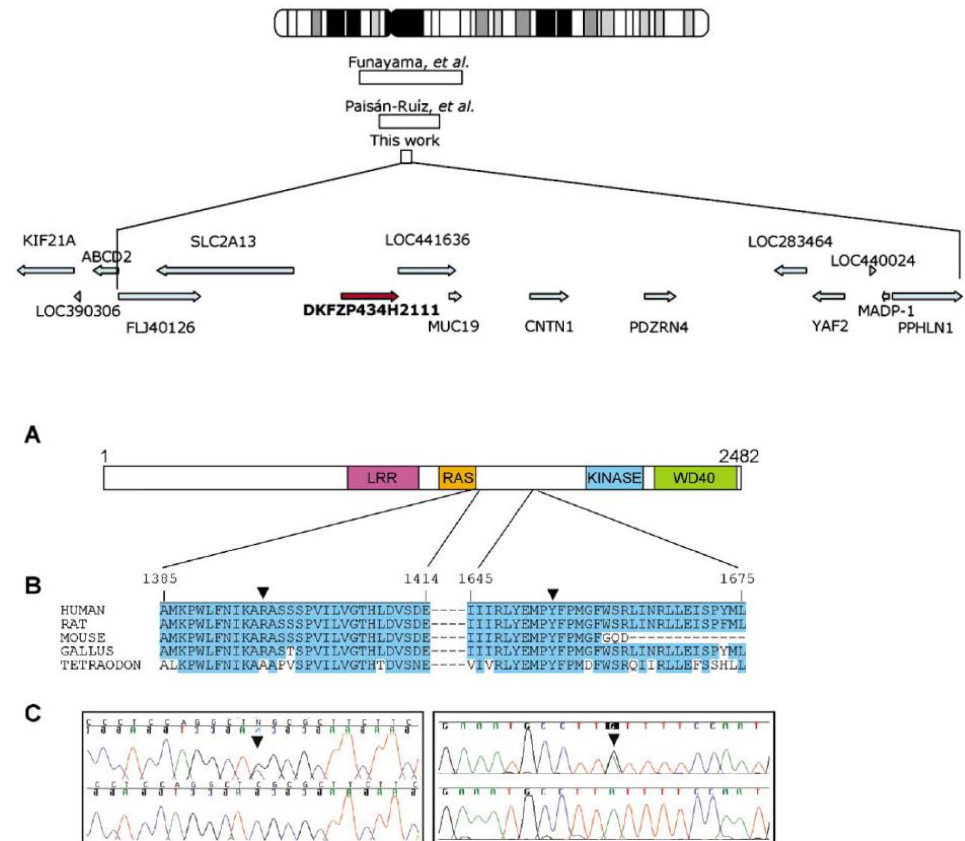


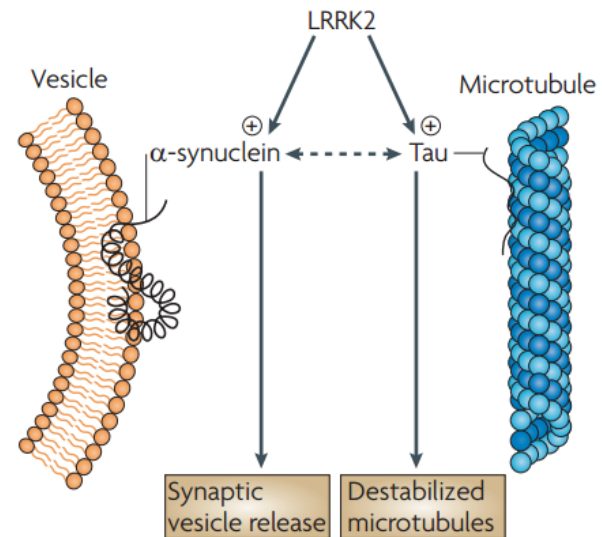
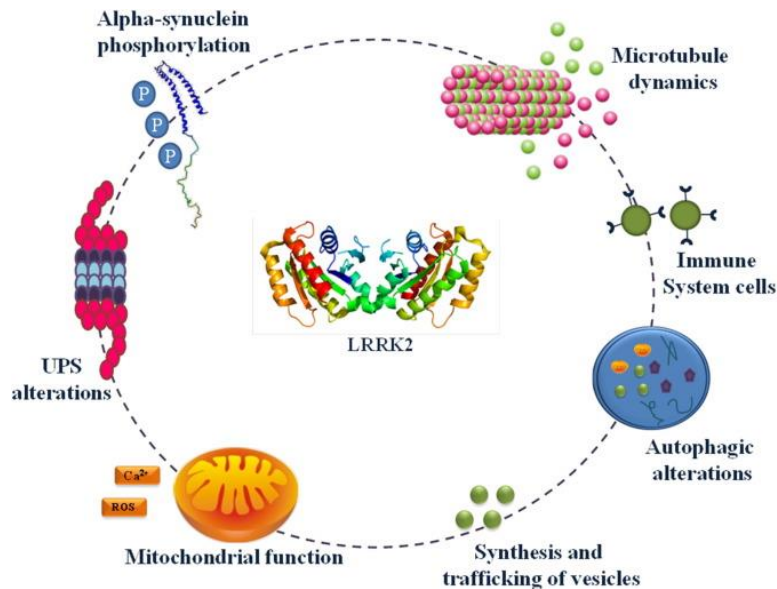
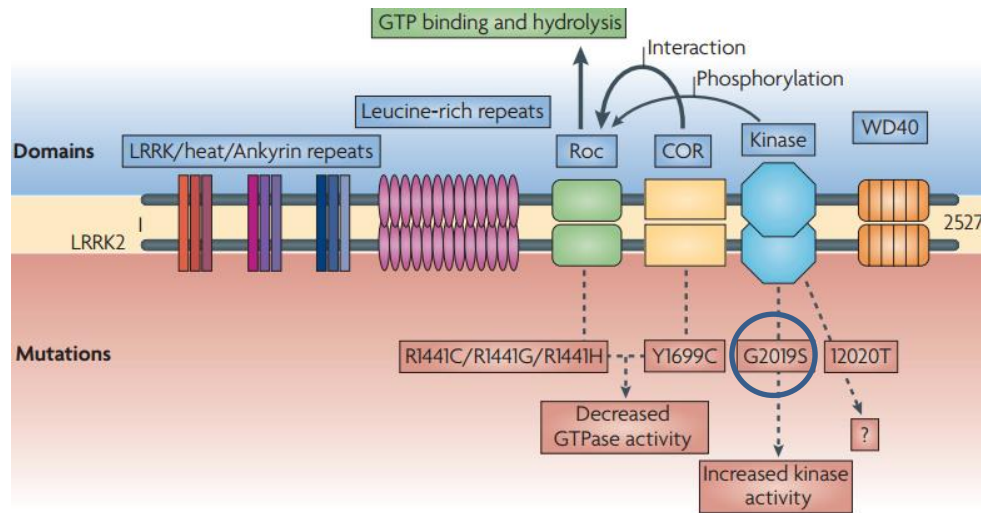
Figure 2. Mutations in Dardarin that Are Linked to *PARK8* PD

(A) Schematic of dardarin structure.

(B) Mutations R1396G and Y1654C are indicated by black arrowheads. Human dardarin protein aligned with other orthologs from rat (XP_235581), mouse (BAC28700), chicken (XP_425418), and tetraodon (CAG05593). Amino acid number is based on the human protein.

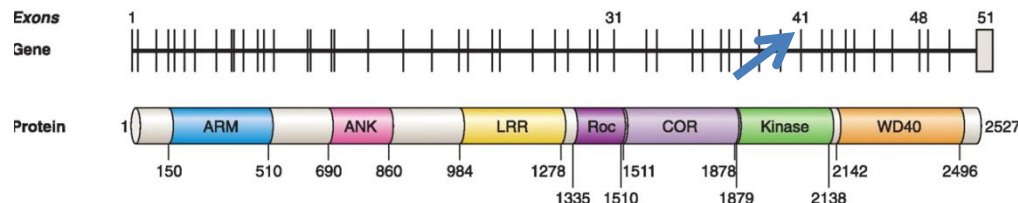
(C) Chromatograms showing mutant sequence (top) and wild-type sequence (bottom) of R1396G (left) and Y1654C (right).

LRRK2 protein = Dardarin protein

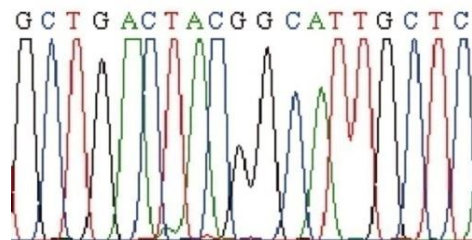


Comprehensive Sequencing of the *LRRK2* Gene in Patients with Familial Parkinson's Disease from North Africa

Barbara Jasinska-Myga, MD, PhD,^{1,2} Jennifer Kachergus, BSc,¹ Carles Vilarino-Güell, PhD,¹ Christian Wider, MD,¹ Alexandra I. Soto-Ortolaza, BSc,¹ Mounir Kefi, MD,³ Lefkos T. Middleton, MD,⁴ Lianna Ishihara-Paul, PhD,⁵ Rachel A. Gibson, PhD,⁵ Rim Amouri, PhD,³ Samia Ben Yahmed, MD,³ Samia Ben Sassi, MD,³ Mourad Zouari, MD,³ Ghada El Euch, MD,³ Owen A. Ross, PhD,¹ Faycal Hentati, MD,³ and Matthew J. Farrer, PhD^{1*}



Wild type



Mutant

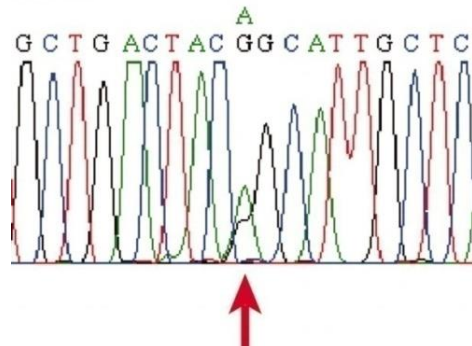


TABLE 2. *LRRK2* variants in probands with familial PD (n = 92) from Tunisia

Exon	dbSNP number	DNA change	Protein change	Protein domain	Variant carriers	
					Heterozygous	Homozygous
1	rs2256408	c.149G>A	p.R50H	N-Terminal	1 (1.1)	91 (98.9)
4	rs33995463	c.356T>C	p.L119P	N-Terminal	2 (2.2)	0 (0.0)
5	rs10878245	c.457T>C	p.L153L	N-Terminal	35 (38.5)	27 (29.7)
11	rs34594498	c.1256C>T	p.A419V	N-Terminal	1 (1.1)	0 (0.0)
14	rs7308720	c.1653C>G	p.N551K	N-Terminal	12 (13.0)	1 (1.1)
8	rs10878307	c.2167A>G	p.I723V	N-Terminal	12 (13.5)	1 (1.1)
21	rs58559150 ^a	c.2769G>C	p.Q923H	N-Terminal	1 (1.1)	0 (0.0)
22	rs7966550	c.2857T>C	p.L953L	N-Terminal	20 (22.0)	1 (1.1)
28	rs4640000	c.3784C>G	p.P1262A	LRR	1 (1.1)	0 (0.0)
29	rs17466213 ^a	c.4111A>G	p.I1371V	Roc	2 (2.2)	1 (1.1)
30	rs7133914	c.4193G>A	p.R1398H	Roc	15 (16.3)	2 (2.2)
30	rs11175964	c.4269G>A	p.K1423K	Roc	8 (8.7)	0 (0.0)
32	rs35507033	c.4541G>A	p.R1514Q	COR	1 (1.1)	0 (0.0)
34	rs1427263	c.4872C>A	p.G1624G	COR	37 (40.2)	47 (51.1)
34	rs11176013	c.4911A>G	p.K1637K	COR	42 (91)	32 (34.8)
34	rs35303786	c.4937T>C	p.M1646T	COR	1 (1.1)	0 (0.0)
34	rs11564148	c.4939T>A	p.S1647T	COR	36 (39.1)	14 (15.2)
37	rs10878371	c.5457T>C	p.G1819G	COR	41 (46.1)	33 (36.3)
41	rs34637584	c.6055G>A	p.G2019S	MAPK	27 (29.3)	9 (9.8)
42	rs33995883	c.6241A>G	p.N2081D	MAPK	7 (7.6)	0 (0.0)
43	rs10878405	c.6324G>A	p.E2108E	MAPK	32 (34.8)	16 (17.4)
44	rs35658131 ^a	c.6566A>G	p.Y2189C	WD40	2 (2.2)	0 (0.0)
48	rs33962975	c.7155A>G	p.G2385G	WD40	17 (18.7)	1 (1.1)
49	rs3761863	c.7190T>C	p.M2397T	WD40	34 (36.9)	45 (48.9)
49	rs60545352 ^b	c.7224G>A	p.M2408I	WD40	1 (1.1)	0 (0.0)

LRRK2 Gly2019Ser penetrance in Arab-Berber patients from Tunisia: a case-control genetic study

Mary M Hulihan, Lianna Ishihara-Paul, Jennifer Kachergus, Liling Warren, Rim Amouri, Ramu Elango, Rab K Prinjha, Ruchi Upmanyu, Mounir Kefi, Mourad Zouari, Samia Ben Sassi, Samia Ben Yahmed, Ghada El Euch-Fayeche, Paul M Matthews, Lefkos T Middleton, Rachel A Gibson, Fayçal Hentati, Matthew J Farrer

	Overall		LRRK2 Gly2019Ser	
	Sporadic PD	Controls	Sporadic PD	Controls
N	238	371	72 (30%)	7 (2%)
Number of men (%)	116 (49%)	191 (51%)	39 (54%)	4 (57%)
Age (years)	63.4	56.0	64.1	55.1
Median age (IQR)	66 (25-85)	55 (29-90)	66 (40-82)	54 (40-70)
Mean age at onset (SD) years	57 (12.5)	..	58 (10.7)	..
Median age at onset (IQR) years	60 (20-82)	..	60 (34-79)	..

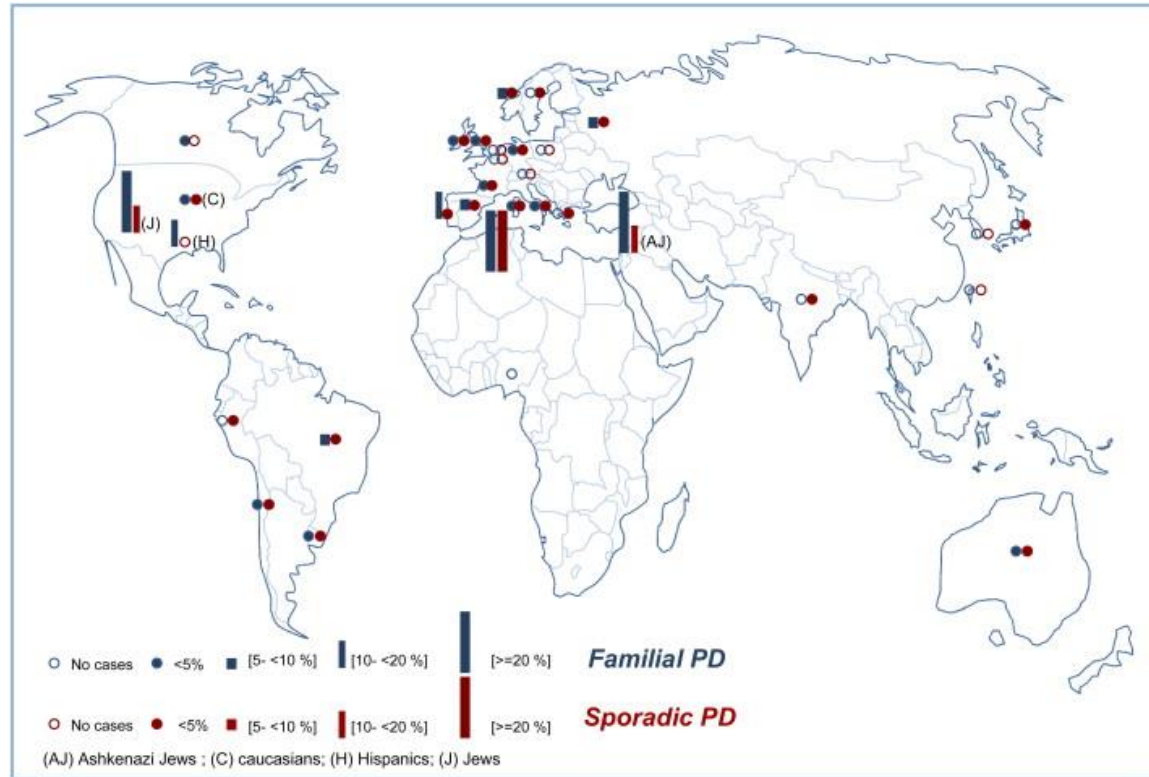
Table 1: Demographics of patients and controls

THE LANCET Neurology



Important conceptual implication
Same etiology for familial and sporadic PD

Worldwide frequency of G2019S LRRK2 mutation in Parkinson's disease



A founding LRRK2 haplotype shared by North Africans, US, European and Middle Eastern families with Parkinson's disease.

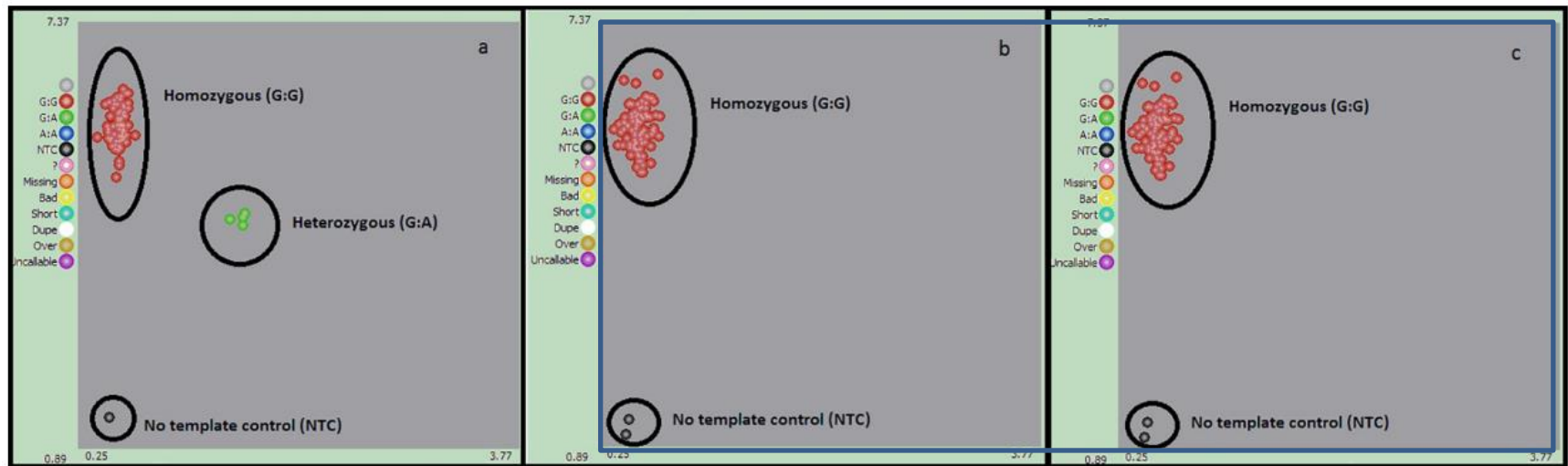
Common founder of the mutation dated to 2600 (95% CI: 1950–3850) years ago.

RESEARCH ARTICLE

Leucine rich repeat kinase 2 (LRRK2) GLY2019SER mutation is absent in a second cohort of Nigerian Africans with Parkinson disease

Njideka U. Okubadejo¹*, Mie Rizig², Oluwadamilola O. Ojo¹, Hallgeir Jonvik²,
Olajumoke Oshinaike³, Emmeline Brown², Henry Houlden²

126 PD patients
106 sporadic and 20 familial cases



KASP assay cluster plots of the p.G2019S (rs34637584).

Screening *LRRK2* gene mutations in patients with Parkinson's disease in Ghana

Roberto Cilia · Francesca Sironi · Albert Akpalu · Momodou Cham ·
Fred Stephen Sarfo · Tiziana Brambilla · Alba Bonetti ·
Marianna Amboni · Stefano Goldwurm · Gianni Pezzoli

	PD patients (<i>n</i> = 54)	Healthy subjects (<i>n</i> = 46)
Age at examination [mean \pm SD (range)], years	65 \pm 12 (34–89)	63 \pm 11 (43–85)
Male gender, %	61%	56%
Age at PD onset [mean \pm SD (range)], years	59.5 \pm 12 (30–83)	–
Disease duration [mean \pm SD (range)], years	6.1 \pm 3.6 (1–20)	–
Tremor dominant/Akinetic-Rigid phenotype	42/12	–
Ethnic origins (Ga Adamgbe/Akan-Ashanti/Ewe/Fanti/Others), %	31/28/29/10/2	32/31/26/7/4
Family history of PD or tremor in a first-degree relative, <i>n</i> (%) ^a	10 (19)	–
UPDRS III [mean \pm SD (range)]	36 \pm 15 (9–74)	–
Hoehn and Yahr stage [mean \pm SD (range)]	2.4 \pm 0.7 (1–4)	–

LRRK2 (exons 31 and 41) screened by sequence analysis

No Mutations in exons 31 and 41 of LRRK2

Analysis of *LRRK2*, *SNCA*, *Parkin*, *PINK1*, and *DJ-1* in Zambian patients with Parkinson's disease

Ekaterina Yonova-Doing^a, Masharip Atadzhanov^{b,**}, Marialuisa Quadri^a, Paul Kelly^b, Nyambura Shawa^b, Sheila T.S. Musonda^b, Erik J. Simons^a, Guido J. Breedveld^a, Ben A. Oostra^a, Vincenzo Bonifati^{a,*}

38 PD patients/ 32 sporadic

Direct sequencing of *LRRK2*

Exons 29 to 48 in 38 PD patients, all exons in 22 PD patients

Coding variants in the *LRRK2* gene.

Position	dbSNP accession N.	Variant allele frequency in dbSNP	Nucleotide change	Protein change	Homozygous PD carriers	Heterozygous PD carriers	Variant allele frequency in the patient cohort
exon 1 ^a	rs2256408	0.892	c.149G > A	p.Arg50His	18	4	0.909
exon 5 ^a	rs10878245	0.333	c.457T > C	p.Leu153Leu	6	1	0.295
exon 8 ^a	rs17490713	0.050	c.867C > T	p.Ans289Ans	0	1	0.023
exon 14 ^a	rs7308720	0.112	c.1653C > G	p.Asn551Lys	2	8	0.273
exon 30	rs7133914	0.192	c.4193G > A	p.Arg1398His	1	10	0.154
exon 31	novel		c.4391C > G	p.Ala1464Gly	0	1	0.013
exon 34	rs1427263	0.801	c.4872C > A	p.Gly1624Gly	31	7	0.885
exon 34	rs11176013	0.580	c.4911A > G	p.Lys1637Lys	18	17	0.679
exon 34	rs11564148	0.192	c.4939T > A	p.Ser1647Thr	2	12	0.205
exon 35	rs79909111	n.a.	c.5163A > G	p.Ser1721Ser	0	3	0.038
exon37	rs10878371	0.580	c.5457T > C	p.Gly1819Gly	18	16	0.684
exon 43	rs10878405	0.097	c.6324G > A	p.Glu2108Glu	0	7	0.090
exon 48	rs33962975	n.a.	c.7155A > G	p.Gly2385Gly	0	3	0.038
exon 49 ^a	rs3761863	0.442	c.7190T > C	p.Met2397Thr	4	14	0.500

^a Exon sequenced in 22 patients.

SHORT COMMUNICATION



Frequency of the *LRRK2* G2019S mutation in South African patients with Parkinson's disease

Nicola du Toit¹ • Riaan van Coller² • David G. Anderson³ • Jonathan Carr⁴ • Soraya Bardien¹

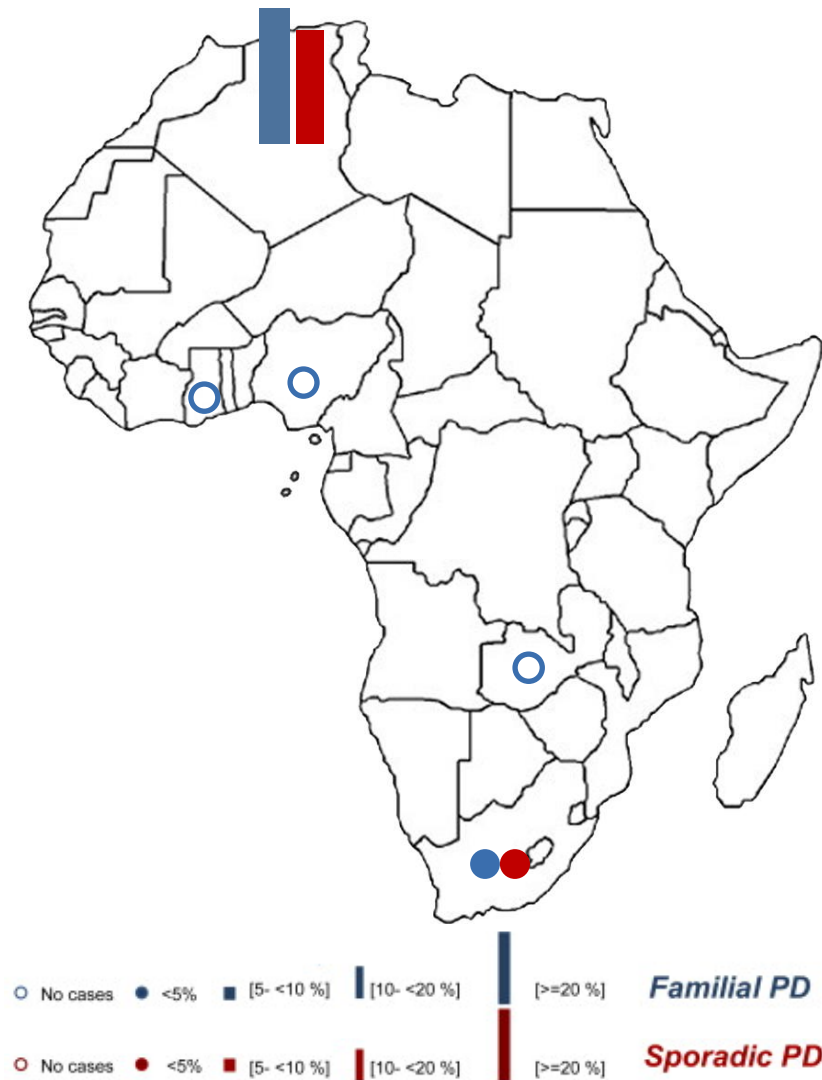
647 PD patients/ 91 of African ancestry
HRM analysis

Demographics of South African Parkinson's disease patients harbouring the *LRRK2* G2019S mutation

Family number	Patient ID number	Zygosity	Sex	Ancestry	AAO (years)	Family history and mode of inheritance	
ZA40	60.47	Heterozygous	Female	Mixed ancestry	47	+	AD
ZA85	68.06	Heterozygous	Female	Ashkenazi Jewish	42	+	AD
ZA133	81.64	Heterozygous	Female	Ashkenazi Jewish	70	–	Unknown
ZA154	82.47	Heterozygous	Male	Ashkenazi Jewish	63	–	Unknown
ZA206	84.25	Homozygous	Female	Ashkenazi Jewish	58	+	AD
ZA456	11.640	Heterozygous	Female	Ashkenazi Jewish	70	+	AD
ZA523	12.482	Heterozygous	Male	Ashkenazi Jewish	48	–	Unknown
ZA594	13.002	Heterozygous	Female	Ashkenazi Jewish	55	+	AD

G2019S mutation frequency = 1.2% (8/647)
No cases in Black or Afrikaner

LRRK2 PD in Africa



Is LRRK2 PD and iPD the same disease ?

A comparative study of Parkinson's disease and leucine-rich repeat kinase 2 p.G2019S parkinsonism

Joanne Trinh^{a,*}, Rim Amouri^b, John E. Duda^c, James F. Morley^c, Matthew Read^d, Alan Donald^a, Carles Vilariño-Güell^a, Christina Thompson^a, Chelsea Szu Tu^a, Emil K. Gustavsson^a, Samia Ben Sassi^b, Emna Hentati^b, Mourad Zouari^b, Emna Farhat^b, Fatma Nabli^b, Faycel Hentati^b, Matthew J. Farrer^a

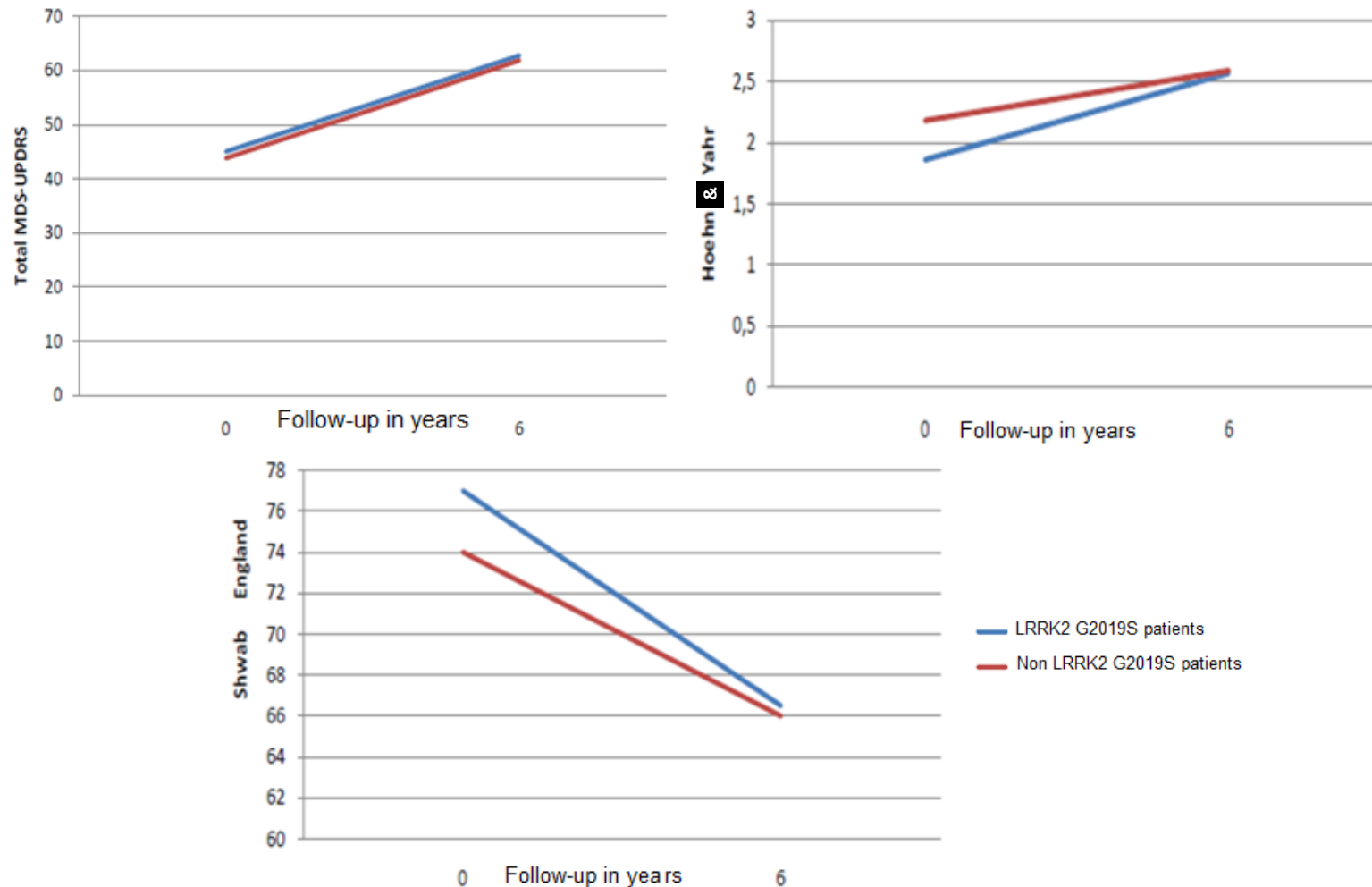


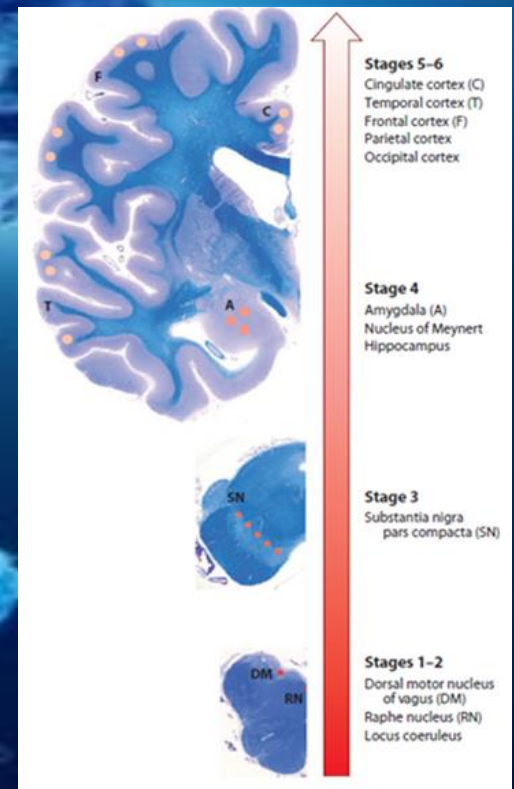
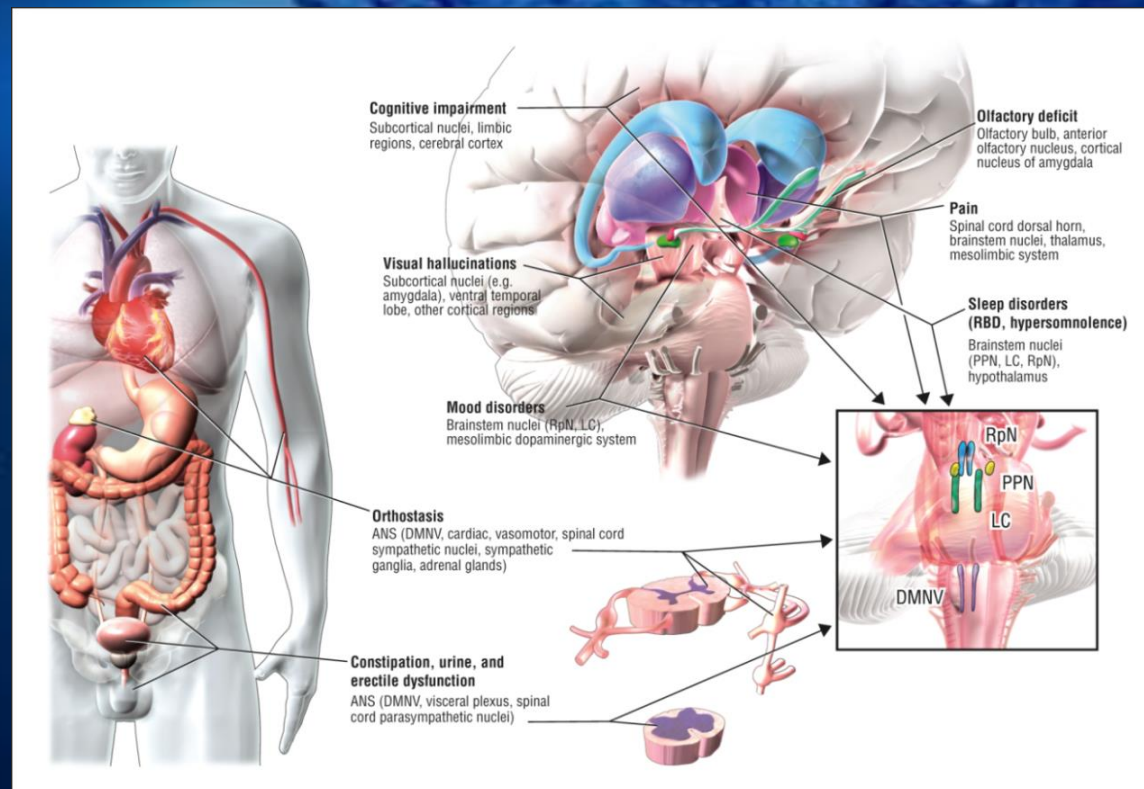
Table 3
Clinical summary of patients

<i>LRRK2</i> carrier status	Homozygous	Heterozygous	iPD	<i>p</i> -values
N	32	177	324	
Mean age of onset (SD)	54.5 (12.4)	57.3 (11.9)	56.2 (13.8)	0.46
Median age of onset (IQR)	56 (40–72)	58 (41–75)	58 (38–78)	
First symptom (%)				
Tremor	23 (71.9%)	135 (76.3%)	265 (81.5%)	0.53
Gait or balance deterioration	4 (12.5%)	23 (13.0%)	26 (8.0%)	
Muscle cramping or dystonia	2 (6.2%)	5 (2.8%)	7 (2.2%)	
Shoulder stiffness	0	5 (2.8%)	8 (2.5%)	
Other	3 (9.4%)	7 (4.0%)	10 (3.1%)	
NA	0	2 (1.1%)	8 (2.5%)	
PD phenotype (%)				
Mixed	22 (69%)	101 (57%)	192 (59.1%)	0.29
Akinetic rigid	3 (9.4%)	34 (19.2%)	68 (21.0%)	
Tremor dominant	6 (19%)	31 (17.5%)	62 (19.1%)	
NA	1 (3.1%)	11 (6.2%)	2 (0.6%)	
Hoehn and Yahr (SD)				
On (SD, n)	2.5 (0.9, 20)	2.1 (0.8, 70)	1.9 (1.0, 126)	0.21
Off (SD, n)	1.6 (0.9, 8)	2.3 (1.1, 84)	2.3 (0.9, 123)	
UPDRS-III score (SD)				
On (SD, n)	34.0 (21.1, 20)	36.7 (16.4, 70)	33.3 (19.5, 128)	0.45
Off (SD, n)	45.2 (19.8, 8)	49.0 (21.9, 84)	47.4 (17.2, 123)	

Motor Phenotype of LRRK2-Associated Parkinson's Disease: A Tunisian Longitudinal Study

Fatma Nabli, MD,^{1*} Samia Ben Sassi, MD,¹ Rim Amouri, PhD,¹ John E. Duda, MD,² Matthew J. Farrer, PhD,³ and Fayçal Hentati, MD¹





A comparative study of Parkinson's disease and leucine-rich repeat kinase 2 p.G2019S parkinsonism

Joanne Trinh^{a,*}, Rim Amouri^b, John E. Duda^c, James F. Morley^c, Matthew Read^d, Alan Donald^a, Carles Vilariño-Güell^a, Christina Thompson^a, Chelsea Szu Tu^a, Emil K. Gustavsson^a, Samia Ben Sassi^b, Emna Hentati^b, Mourad Zouari^b, Emna Farhat^b, Fatma Nabli^b, Faycel Hentati^b, Matthew J. Farrer^a

Non-motor symptoms

Summary of autonomic assessments compared between *LRRK2* parkinsonism and iPD

Olfactory function assessed using Sniffin Sticks

Gastrointestinal (SD) Urinary (SD) Cardiovascular (SD) Thermoregulatory (SD)	Identification	Comparison of sleep scales among <i>LRRK2</i> parkinsonism and iPD.			
			<i>LRRK2</i>	iPD	p-value
	Discrimination	Epworth total score			
	Threshold	On state (SD)	5.35 (4.67)	5.25 (4.90)	0.98
	Total Score	Off state (SD)	4.75 (4.48)	4.88 (5.19)	
	Restless legs				
	On state (%)	9/75 (12%)	15/118 (13%)	0.75	
	Off state (%)	6/81 (7.4%)	11/113 (9.7%)		
	REM sleep disorder				
	On state (%)	12/75 (16%)	34/118 (29%)	0.001	
	Off state (%)	14/81 (17%)	40/113 (35%)		
	Sleep apnea				
	On state (%)	7/75 (9.3%)	10/118 (8.5%)	0.65	

Cognitive dysfunction in Tunisian LRRK2 associated Parkinson's disease

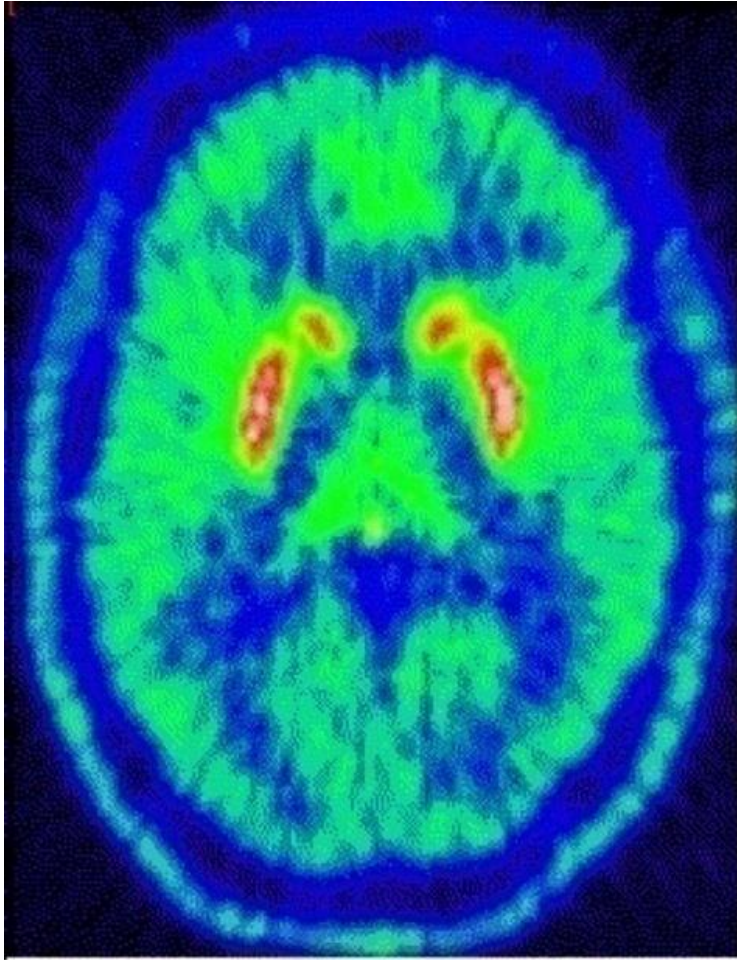
Samia Ben Sassi^{a,*}, Fatma Nabli^a, Emna Hentati^a, Houda Nahdi^a, Meriam Trabelsi^a, Hela Ben Ayed^a, Rim Amouri^a, John Eric Duda^b, Matthew John Farrer^c, Fayçal Hentati^a

Table 2

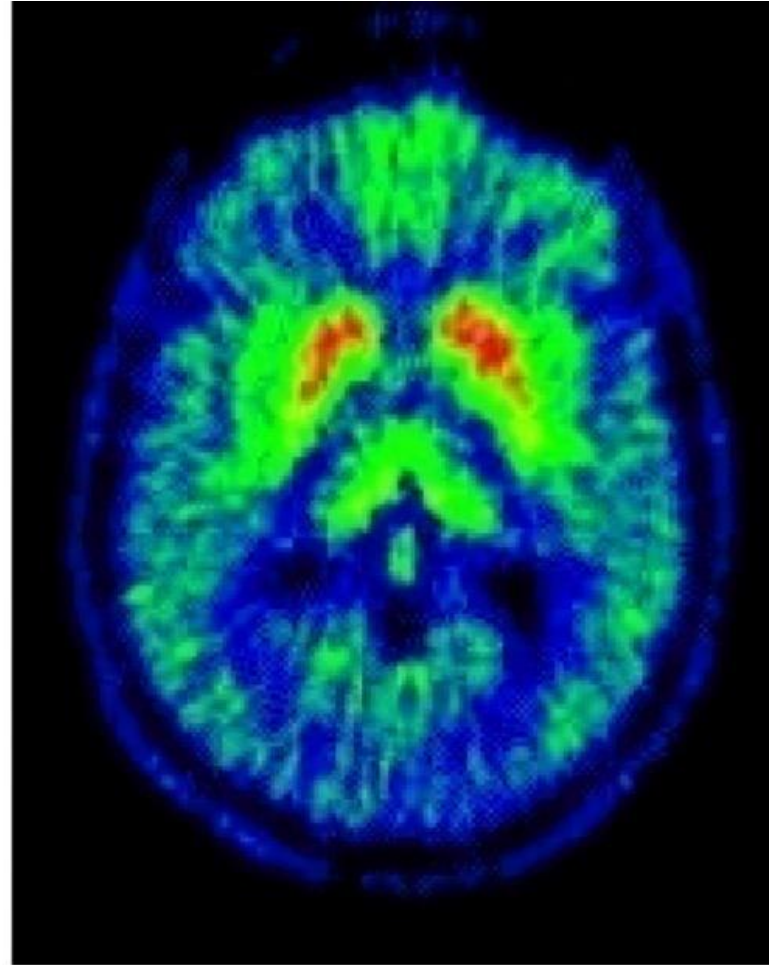
Cognitive assessment of Parkinson's disease patients with and without G2019S LRRK2 mutation.

	G2019S carriers	G2019S non-carriers
	N = 55	N = 55
MMSE score, ≤24	25.5 ± 3.2, 29%	25.16 ± 2.85, 32%
Orientation	8.7 ± 1.7	8.4 ± 1.5
Registration	2.9 ± 0.2	3
Attention and calculation	4.5 ± 1.2	4.6 ± 1.1
Recall	2 ± 0.9	1.7 ± 1
language	6.3 ± 1.1	6.3 ± 0.9
Copying two pentagons	0.2 ± 0.4	0.2 ± 0.4
FAB score, < 13	10.6 ± 4.5, 54%	9.4 ± 3.9, 66%
Similarities	1.8 ± 1.2	1.5 ± 1
Lexical fluency	1.0 ± 1	1.4 ± 1
Motor series	1.9 ± 1	1.8 ± 1.2
Conflicting instructions	1.5 ± 1.3	1.2 ± 1
Go-No-Go	1.3 ± 1.1	1.2 ± 1.3
6-picture test	N = 35	N = 38
free recall/identification	4.8 ± 0.9/5.4 ± 0.9	4.1 ± 1.4/5.2 ± 1.3
MOCA, < 26	N = 20	N = 17
	21.8 ± 4.3, 65%	21.8 ± 3.7, 69%
Visuospatial and executive	2.9 ± 1.6	3.2 ± 1.4
Naming	2.6 ± 0.7	2.9 ± 0.3
Attention	4.0 ± 1.6	4.4 ± 1.2
Language	1.7 ± 1	1.5 ± 0.8
Abstraction	1.7 ± 0.6	1.3 ± 0.8
Delayed recall	2.2 ± 1.4	2 ± 1.8
Orientation	5.9 ± 0.4	5.9 ± 0.3

^{18}F -dopa PET Scan



Control Subject

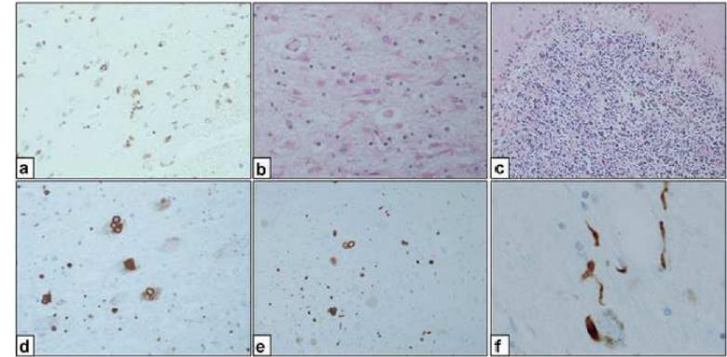


LRRK2 PD patient

LRRK2 Neuropathology

Summary of *LRRK2* autopsy reports

Report	Autopsies (n)	Genotype (n)	Phenotype (n)	Pattern of neuronal loss	LB, LN pathology (n)	LB distribution-Braak stage (n)	Tau pathology-NFT stage (n)	Other inclusions (n)
Gilks, 2005 ³⁴	3	G2019S (3)	PD (3)	SNpc, LC	+ (3)	3 (1) 4 (2)	Sparse (1) - (2)	-
Gaig, 2008 ³⁵ Gaig, 2007 ³⁶ Gomez, 2010 ⁴⁰	3	G2019S (3)	PD (3)	SNpc, LC	+ (2) - (1)	4 (1) 5 (1) - (1)	I (1) II (1) III (1)	-
Rajput, 2006 ³⁷	1	G2019S (1)	PD (1)	SNpc mild	- (1)	-	IV (1)	PSP-like
Ross, 2006 ³⁸	10	G2019S (10)	PD (8) Dementia (3/8), Cognitive decline (2/8) AD (1) Control (1)	SNpc, LC	+ (8) - (2)	3 (4) 4 (3) 6 (1) - (2)	- (3) I (1) III (4) AD (2)	-
Giasson, 2006 ³⁹	3	G2019S (3)	EOPD (1), PD (2) Dementia (1/3)	SNpc, LC	+ (2) - (1)	4 (1) 5 (1) - (1)	I (1) III (1) AD (1)	-
Silveira, 2008 ⁴¹	4	G2019S (4)	PD (4)	SNpc, LC, Olfactory bulb	+ (4)	5 (4)	II (4)	Olfactory bulb LBs (4)
Daschel, 2007 ⁴²	1	G2019S (1)	Dementia (1)	Hippocampus	- (1)	- (1)	- (1)	FTLD-U
Poulopoulos ⁴³	3	G2019S (3)	EOPD (2), PD (1) Dementia (2/3)	SNpc, LC	+ (3)	4 (2) 6 (1)	Sparse (2) AD (1)	-
Hasegawa, 2009 ⁴⁵ Hasegawa, 1997 ⁴⁴	8	I2020T (8)	PD (8)	SNpc, SNpr, LC spared	- (7) + (1)	- (7) 3 (1)	- (8)	GCI (1)
Wszolek 2004 ⁴⁷ Zimprich, 2004 ⁴⁶ Wider 2010 ⁵⁵	6	R1441C (4) Y1699C (2)	PD (6)	SNpc LC	+ (2/4 R1441C) - (4)	4 (1) 6 (1) - (4)	Sparse (1), AD (1 Y1699C), - (4)	PSP-like in 1 (R1441C); TDP-43 in SNpc neurites in 1 (R1441C)
Khan, 2005 ⁴⁸	1	Y1699C (1)	PD (1)	SNpc, LC	+ (1)	3 (1)	II (1)	Olfactory bulb LBs
Marti-Masso, 2009 ⁴⁹	1	R1441G (1)	PD (1)	SNpc > LC	- (1)	-	I (1)	a-B crystalline in SN
Gaig, 2008 ³⁵	1	R1441R (1)	PD Dementia (1)	SNpc	+ (1)	No details	No details	-
Giordana, 2007 ⁵⁰	1	I1371V (1)	PD cognitive decline (1)	SNpc > LC	+ (1)	4 (1)	II (1)	-
Covy, 2009 ⁵¹	2	R793M (1) L1165P (1)	PD (2) Dementia (1/2)	SNpc, LC	+ (2)	4 (2)	II (1) III (1)	TDP-43 in TC (2)
Puschmann, 2011 ⁵²	1	N1437H (1)	PD (1)	SNpc > LC	+ (1)	5 (1)	Sparse (1)	Diffuse, atypical ubiquitin+ inclusions



LRRK2 Gly2019Ser penetrance in Arab-Berber patients from Tunisia: a case-control genetic study

Mary M Hulihan, Lianna Ishihara-Paul, Jennifer Kachergus, Liling Warren, Rim Amouri, Ramu Elango, Rab K Prinjha, Ruchi Upmanyu, Mounir Kefi, Mourad Zouari, Samia Ben Sassi, Samia Ben Yahmed, Ghada El Euch-Fayeche, Paul M Matthews, Lefkos T Middleton, Rachel A Gibson, Fayçal Hentati, Matthew J Farrer

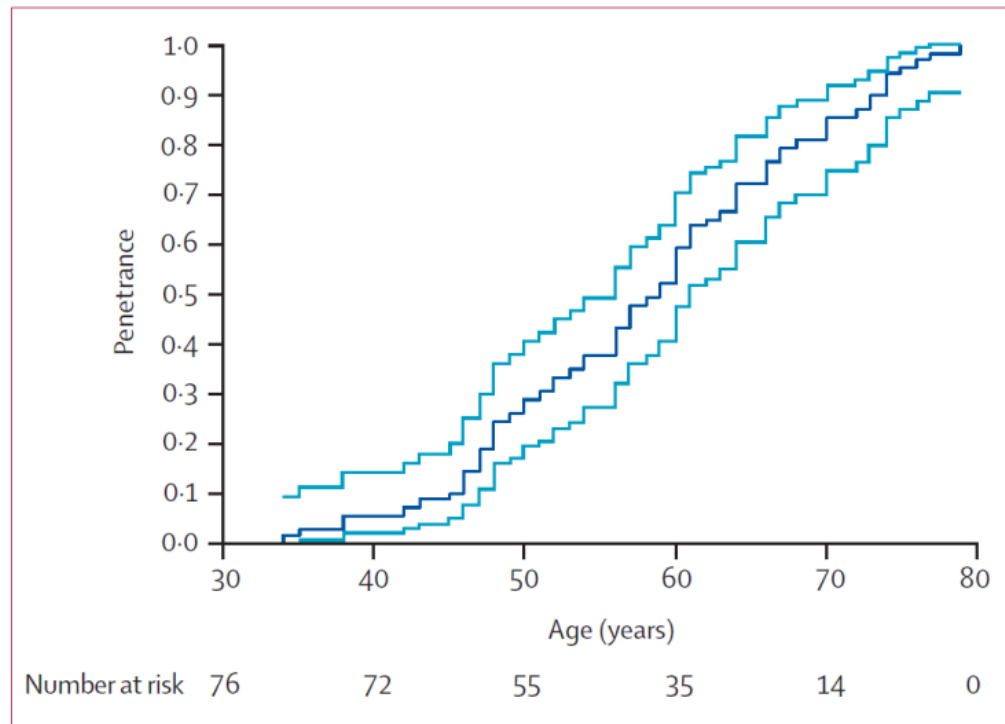
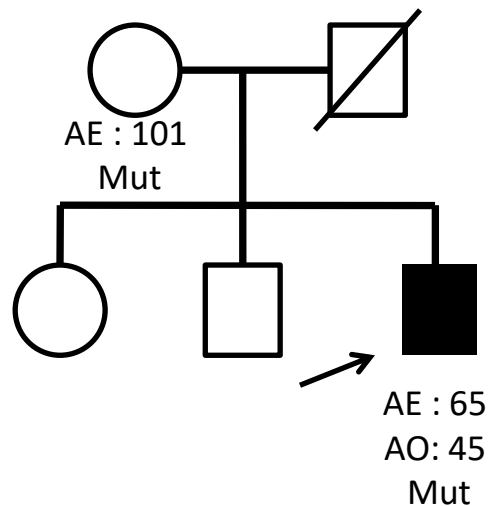
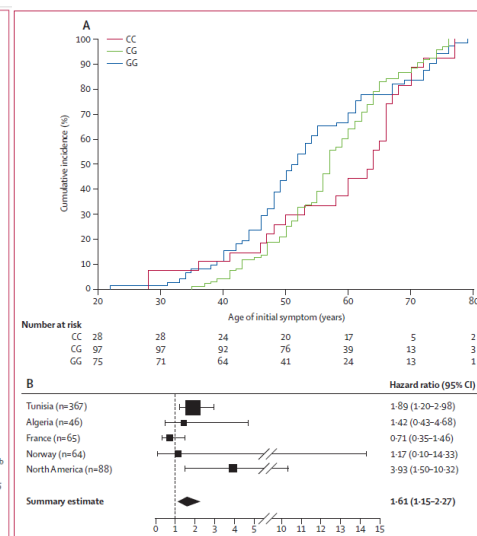
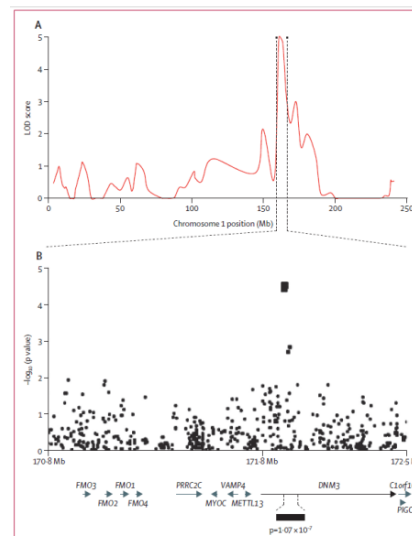
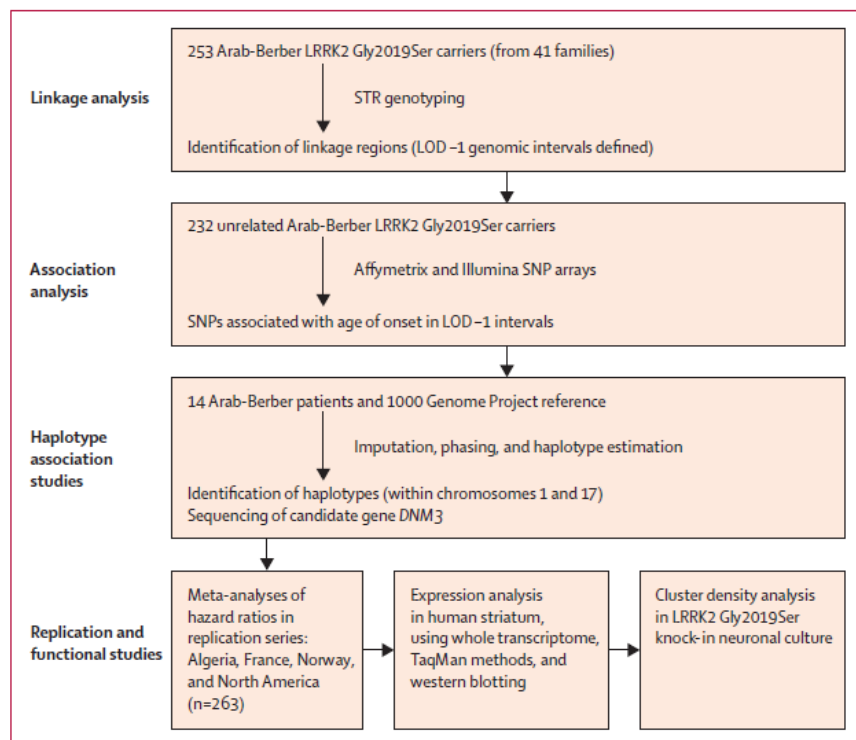


Figure: Kaplan-Meier curve of age-associated penetrance of PD in carriers of LRRK2 Gly2019Ser

DNM3 and genetic modifiers of age of onset in LRRK2 Gly2019Ser parkinsonism: a genome-wide linkage and association study

Joanne Trinh, Emil K Gustavsson, Carles Vilariño-Güell, Stephanie Bortnick, Jeanne Latourelle, Marna B McKenzie, Chelsea Szu Tu, Ekaterina Nosova, Jaskaran Khinda, Austen Milnerwood, Suzanne Lesage, Alexis Brice, Meriem Tazir, Jan O Aasly, Laura Parkkinen, Hazal Haytural, Tatiana Foroud, Richard H Myers, Samia Ben Sassi, Emna Hentati, Fatma Nabli, Emna Farhat, Rim Amouri, Fayçal Hentati, Matthew J Farrer

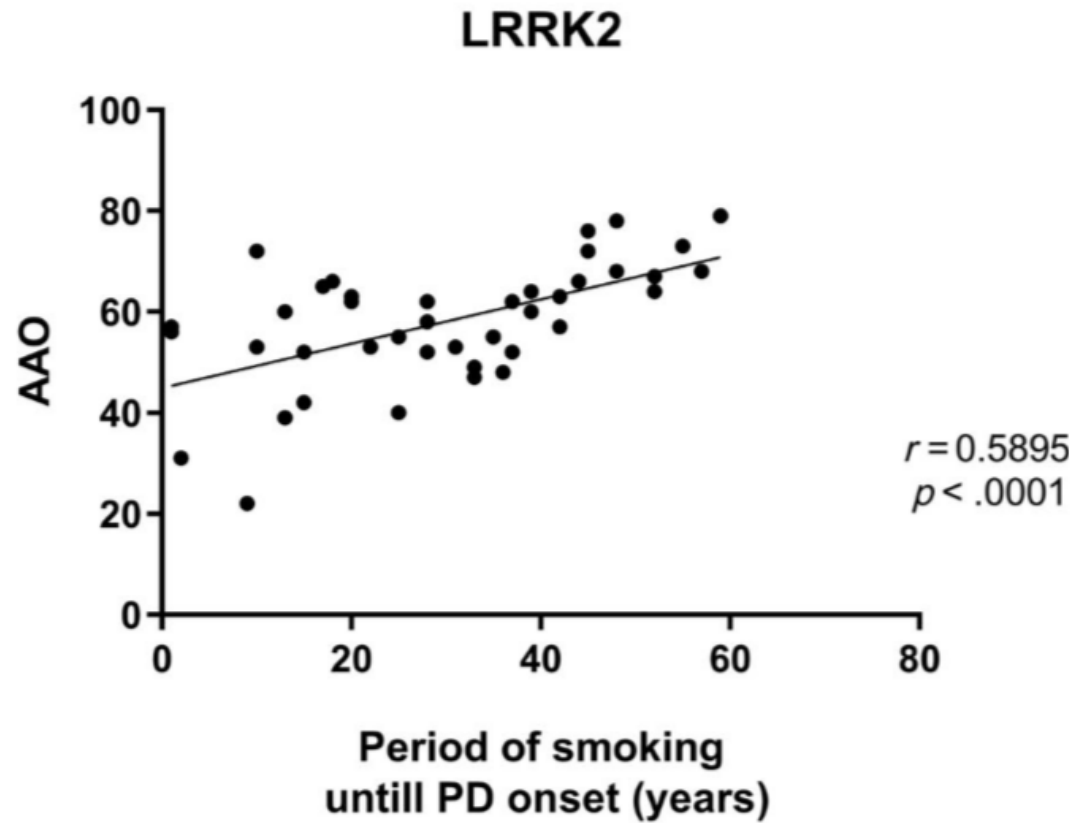


Tagging SNP (rs2421947) in *DNM3*

Median onset of LRRK2 PD in GG carriers 12.5 years younger than that of CC carriers

Age of onset of LRRK2 G2019S is related to Environmental and Lifestyle Factors

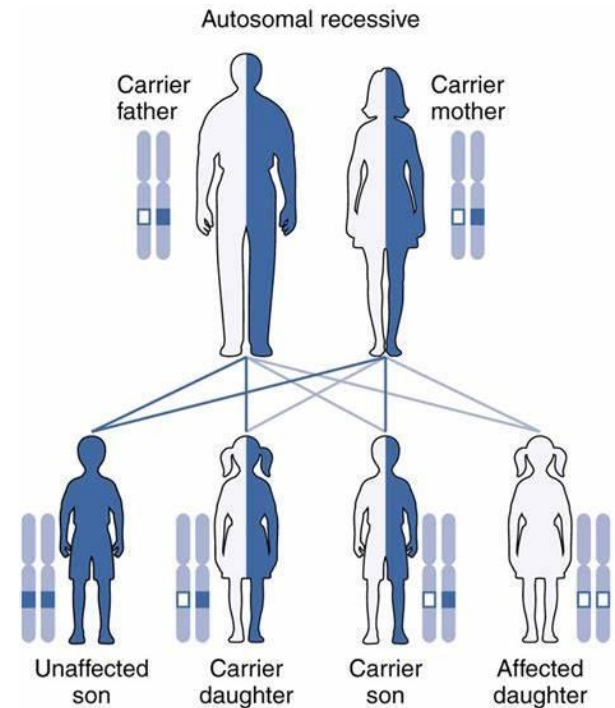
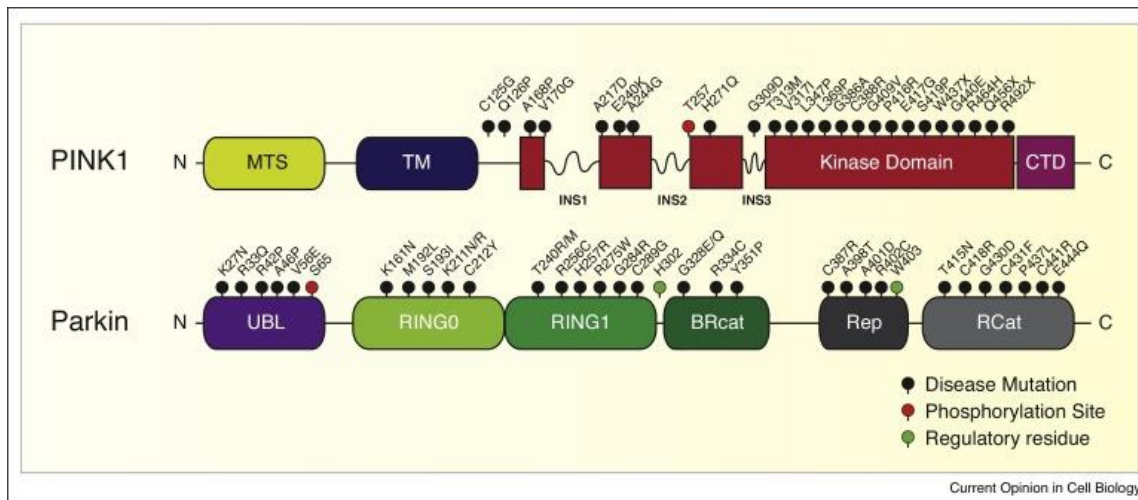
220 IPD / 199 LRRK2
G2019S PD Tunisian
Patients



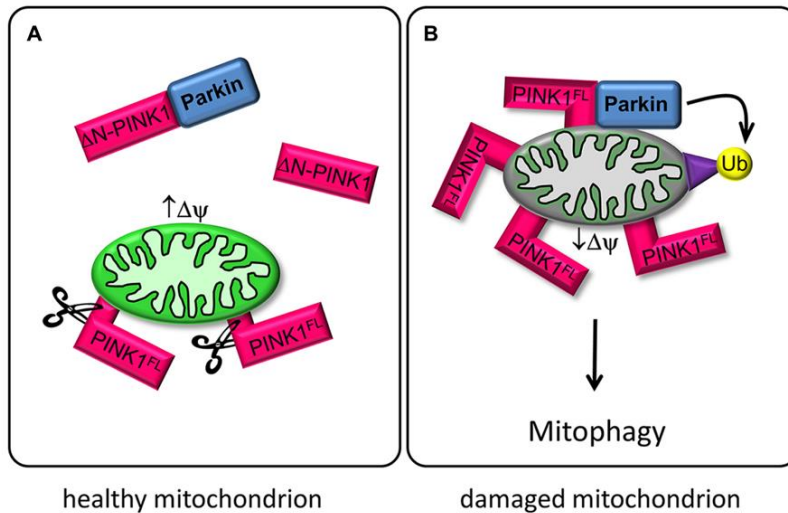
Monogenetic PD

Locus (OMIM)	Location	Full Gene Name Approved by HGNC	HGNC Approved Gene Symbol (OMIM)	Inheritance	Disease onset	Lewy bodies
<i>PARK1</i> (168601)	4q22.1	synuclein alpha	<i>SNCA</i> (163890)	AD	Early-onset, late-onset*	C
<i>PARK2</i> (600116)	6q26	parkin RBR E3 ubiquitin protein ligase	<i>PRKN</i> (602544)	AR	Early-onset	NC
<i>PARK3</i> (602404)	2p13	Parkinson disease 3	<i>PARK3</i> (Unclear)	AD	Late-onset	NC
<i>PARK4</i> (605543)	4q22.1	synuclein alpha	<i>SNCA</i> (163890)	AD	Early-onset	C
<i>PARK5</i> (613643)	4p13	ubiquitin C-terminal hydrolase L1	<i>UCHL1</i> (191342)	AD	Early-onset, late-onset	NC
<i>PARK6</i> (605909)	1p36	PTEN induced putative kinase 1	<i>PINK1</i> (608309)	AR	Early-onset	NC
<i>PARK7</i> (606324)	1p36.23	parkinsonism associated deglycase	<i>PARK7</i> (602533)	AR	Early-onset	NC
<i>PARK8</i> (607060)	12q12	leucine rich repeat kinase 2	<i>LRRK2</i> (609007)	AD	Late-onset	C
<i>PARK9</i> (606693)	1p36.13	ATPase 13A2	<i>ATP13A2</i> (610513)	AR	Early-onset	NC
<i>PARK10</i> (606852)	1p32	Parkinson disease 10	<i>PARK10</i> (Unclear)	Unclear	Late-onset	NC
<i>PARK11</i> (607688)	2q37.1	GRB10 interacting GYF protein 2	<i>GIGYF2</i> (612003)	AD	Late-onset	NC
<i>PARK12</i> (300557)	Xq21-q25	Parkinson disease 12	<i>PARK12</i> (Unclear)	X-linked inheritance	Late-onset	NC
<i>PARK13</i> (610297)	2p13.1	HtrA serine peptidase 2	<i>HTRA2</i> (606441)	AD	Late-onset, early-onset*	NC
<i>PARK14</i> (612593)	22q13.1	phospholipase A2 group VI	<i>PLA2G6</i> (603604)	AR	Early-onset	NC
<i>PARK15</i> (260300)	22q12.3	F-box protein 7	<i>FBXO7</i> (605648)	AR	Early-onset	NC
<i>PARK16</i> (613164)	1q32	Parkinson disease 16	<i>PARK16</i> (Unclear)	Unclear	Late-onset	NC
<i>PARK17</i> (614203)	16q11.2	VPS35, retromer complex component	<i>VPS35</i> (601501)	AD	Late-onset	NC
<i>PARK18</i> (614251)	3q27.1	eukaryotic translation initiation factor 4 gamma 1	<i>EIF4G1</i> (600495)	AD	Late-onset	NC
<i>PARK19</i> (615528)	1p31.3	DnaJ heat shock protein family (Hsp40) member C6	<i>DNAJC6</i> (608375)	AR	Early-onset	NC
<i>PARK20</i> (615530)	21q22.1	synaptojanin 1	<i>SYNJ1</i> (604297)	AR	Early-onset	NC
<i>PARK21</i> (616361)	20p13	transmembrane protein 230	<i>TMEM230</i> (617019)	AD	Late-onset, early-onset*	C
<i>PARK22</i> (616710)	7p11.2	coiled-coil-helix-coiled-coil-helix domain containing 2	<i>CHCHD2</i> (616244)	AD	Late-onset, early-onset*	NC
<i>PARK23</i> (616840)	15q22.2 11p15.4	vacuolar protein sorting 13 homolog C RIC3 acetylcholine receptor chaperone	<i>VPS13C</i> (608879) <i>RIC3</i> (610509)	AR AD	Early-onset Late-onset, early-onset*	NC NC

Parkin and PINK1 PD

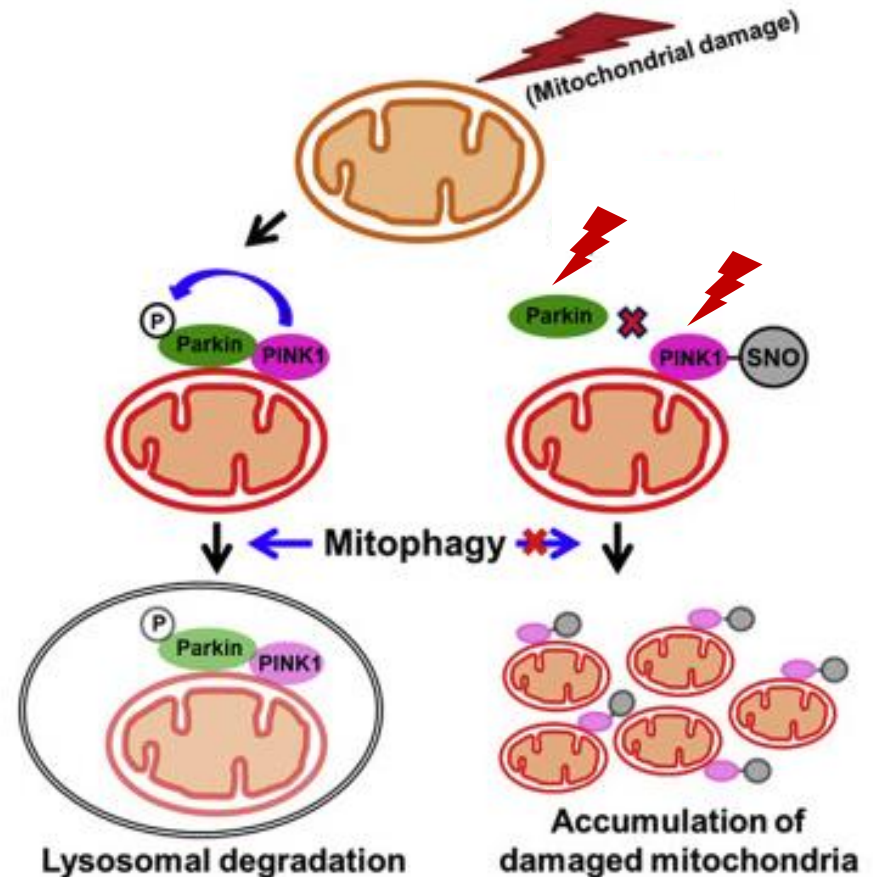


Parkin and PINK1 PD



PARKIN = E3 ubiquitin ligase

PINK1 = Phosphatase and tensin homolog (PTEN)-induced kinase protein 1 (PINK1)
= Mitochondrial kinase



Association between Early-Onset Parkinson's Disease and Mutations in the Parkin Gene

TABLE 1. FREQUENCY OF MUTATIONS IN THE *PARKIN* GENE IN 73 FAMILIES WITH AUTOSOMAL RECESSIVE EARLY-ONSET PARKINSON'S DISEASE AND 100 PATIENTS WITH ISOLATED EARLY-ONSET PARKINSON'S DISEASE. *

NO. OF MUTATIONS	FAMILIES WITH AUTOSOMAL RECESSIVE DISEASE (N=73)		PATIENTS WITH ISOLATED CASES (N=100)	
	NO. OF FAMILIES	NO. OF CONSANGUINEOUS FAMILIES	NO. OF PATIENTS	NO. OF CONSANGUINEOUS PATIENTS
Two	25	5	14	4
One	11†	0	4	0
None identified	37	3	82‡	4
Total no. with mutations (%)	36 (49)	5 (62)	18 (18)	4 (50)

TABLE 2. FREQUENCY OF MUTATIONS IN THE *PARKIN* GENE IN 100 PATIENTS WITH ISOLATED EARLY-ONSET PARKINSON'S DISEASE, ACCORDING TO THE AGE AT ONSET.

AGE AT ONSET	PATIENTS WITH HOMOZYGOUS OR HETEROZYGOUS MUTATIONS	CONSANGUINEOUS PATIENTS WITH HOMOZYGOUS OR HETEROZYGOUS MUTATIONS
	no. of patients/total no. (%)	
≤20 yr	10/13 (77)*	2/3 (67)
21–30 yr	6/23 (26)†	2/2 (100)
31–40 yr	1/49 (2)‡	0/2
41–45 yr	1/15 (7)§	0/1
Total no. of patients (%)	18/100 (18)	4/8 (50)

TABLE 3. CHARACTERISTICS OF PATIENTS WITH PARKINSON'S DISEASE ACCORDING TO THE PRESENCE OR ABSENCE OF MUTATIONS IN THE *PARKIN* GENE.*

CHARACTERISTIC	PATIENTS WITH <i>PARKIN</i> MUTATIONS (N=101)	PATIENTS WITHOUT <i>PARKIN</i> MUTATIONS (N=85)	P VALUE
Sex (F/M)	49/52	31/54	
Age at onset (yr)	32±11	42±11	<0.001
Duration of disease (yr)	17±11	13±11	0.002
Clinical signs at onset (%)			
Micrographia	30	47	0.02
Bradykinesia	63	65	
Tremor	65	75	
Dystonia	42	22	0.02
Asymmetric signs	89	98	0.02
Clinical signs at examination			
Bradykinesia (%)	95	98	
Rigidity (%)	92	99	
Resting tremor (%)	74	80	
Postural tremor (%)	54	47	
Urinary urgency (%)	11	25	0.01
Hyperreflexia (%)	44	21	0.04
No progression or slow rate of progression (%)	88	72	
Motor scale of UPDRS score†			
Without treatment	41±22	43±16	
During treatment	23±18	26±15	
Hoen-Yahr assessment without treatment‡			
Mean stage	3.2±1.0	3.1±0.8	
Interval from onset to stage 2 (yr)	11±9	5±3	
Interval from onset to stage 3 (yr)	19±10	17±8	
Interval from onset to stage 4 (yr)	26±8	33±2	
Interval from onset to stage 5 (yr)	40±19	44	
Mini-Mental State Examination score§	29±3	28±2	
Clinical signs during treatment			
Percent improvement with levodopa	72±20	64±17	0.03
Daily dose of levodopa (mg)	500±340	600±400	
Duration of levodopa treatment			
Months	123±102	111±99	
Years	10	9	
Levodopa-induced dyskinesia			
Percentage of patients	77	63	0.04
Months of treatment	64±65	60±55	
Levodopa-induced fluctuations in symptoms			
Percentage of patients	79	65	
Months of treatment	64±61	61±54	
Dystonia			
Percentage of patients	58	45	
Months of treatment	65±72	54±40	

Parkin analysis in Tunisian patients with familial PD

231 familial PD patients
from 90 families

Direct sequencing PRKN +
Dosage analysis

Table 1 Demographics of patients with genetically undefined, *LRRK2*, *PINK1* and *PRKN* Parkinson's disease

Variable	Genetically undefined PD (n = 107)	<i>LRRK2</i> (n = 73)	<i>PINK1</i> (n = 42)	<i>PRKN</i> (n = 9)
Age (years)	69 (27–96)	70 (38–91)	51 (25–76)	47 (32–79)
Age at onset (years)	60 (9–85)	60 (30–87)	35 (13–59)	32 (21–74)
Gender (Male) (n (%))	66 (62)	36 (49)	22 (52)	3 (33)
Disease duration (years)	6 (<1–49)	6 (1–28)	14 (<1–40)	11 (4–34)

The sample median (minimum-maximum) is given for age, age at onset and disease duration. *LRRK2*, leucine rich repeat kinase 2; *PINK1*, PTEN induced kinase 1; *PRKN*, parkin.

PRKN mutation frequency = 3.9%

PRKN mutations in Nigerians with apparently sporadic PD

57 sporadic PD patients
Early onset in 12%

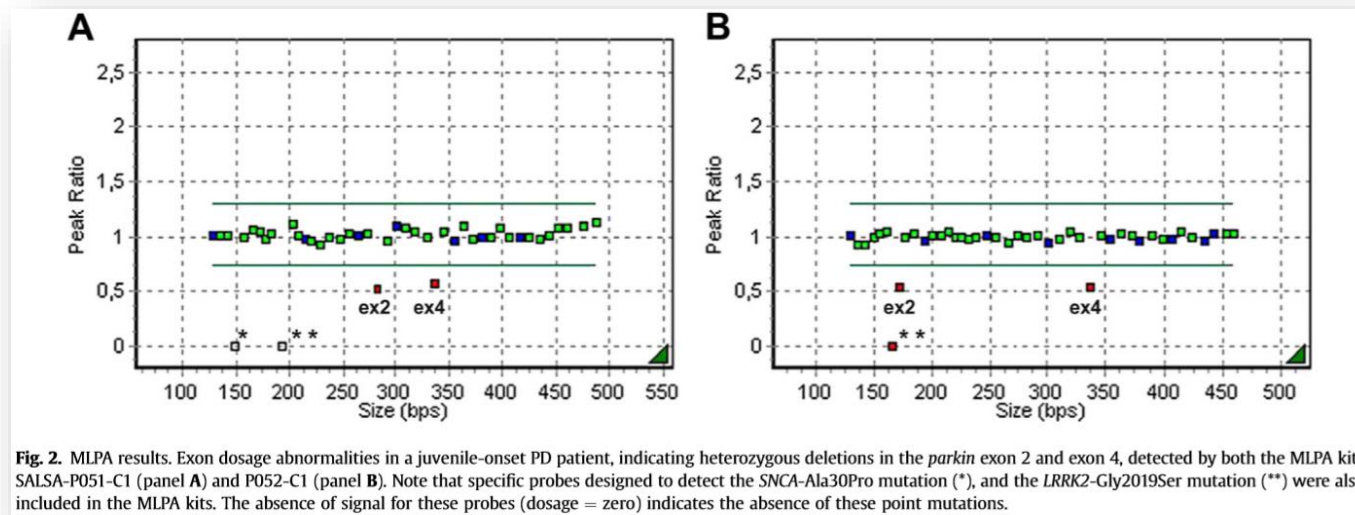
Direct sequencing PRKN +
Dosage analysis

No pathogenic mutations in PRKN

Gene	Heterozygous variants	<i>Parkinson's disease</i>	<i>Control group</i>
		N (%)	N (%)
PARK2	p.E16E; c.G48T	3 (5.3)	1 (2.0)
	p.P37P; c.G111A	8 (14.0)	6 (11.8)
	p.A46T; c.G136A	1 (1.8)	0
	p.P153R; c.C458G	0	1 (2.0)
	p.S167N; c.G500A	4 (7.0)	4 (7.8)
	p.M192L; c.A574G	7 (12.3)	6 (11.8)
	p.L261L; c.A783G	13 (22.8)	14 (27.4)
	p.G319G; c.T957C	5 (8.8)	4 (7.8)
	p.R334H; c.G1001A	1 (1.8)	0
	p.V380L; c.G1138A	2 (3.5)	3 (5.9)
	Homozygous variants		
	p.P37P; c.G111A	1 (1.8)	3 (5.9)
	p.S167N; c.G500A	1 (1.8)	0
	p.L261L; c.A783G	1 (1.8)	3 (5.9)
	p.V380L; c.G1138A	1 (1.8)	1 (2.0)

Parkin analysis in Zambian patients with PD

12 PD patients with early onset (< 50 years-old)
Sequencing of all Parkin exons + MLPA for copy dosage analysis



Juvenile-onset sporadic case, AO = 16/ DD = 24 years

Short communication

Mutations in the parkin gene are a minor cause of Parkinson's disease in the South African population

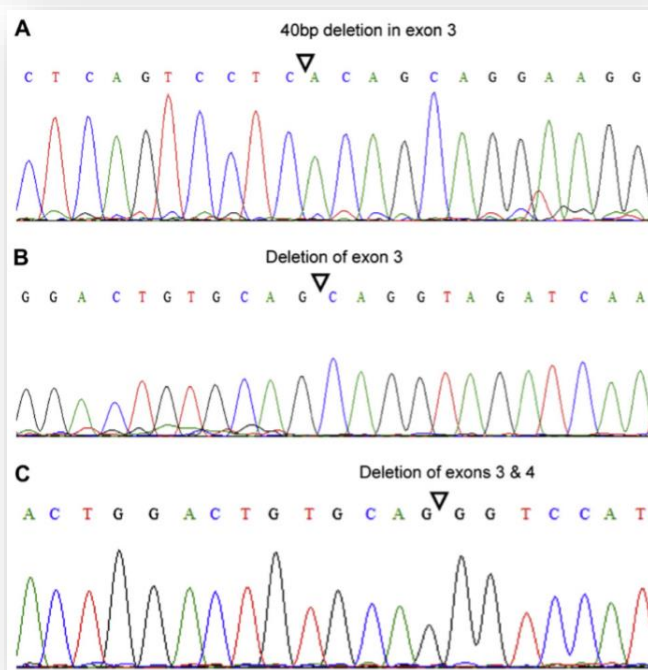
William L. Haylett^a, Rowena J. Keyser^{a,1}, Melissa C. du Plessis^a, Celia van der Merwe^a, Janine Blanckenberg^a, Debbie Lombard^{a,b}, Jonathan Carr^b, Soraya Barden^{a,*}

229 PD patients

7.4% Black

63.3% EAO and/or family history of PD

HRM & MLPA Analyses



PRKN mutation frequency = 3.1% (7/229)

A comparative study of *LRRK2*, *PINK1* and genetically undefined familial Parkinson's disease

Kenya Nishioka,¹ Mounir Kefi,² Barbara Jasinska-Myga,^{1,3} Christian Wider,¹ Carles Vilariño-Güell,¹ Owen A Ross,¹ Michael G Heckman,⁴ Lefkos T Middleton,⁵ Lianna Ishihara-Paul,⁶ Rachel A Gibson,⁶ Rim Amouri,² Samia Ben Yahmed,² Samia Ben Sassi,² Mourad Zouari,² Ghada El Euch,² Matthew J Farrer,¹ Faycal Hentati²

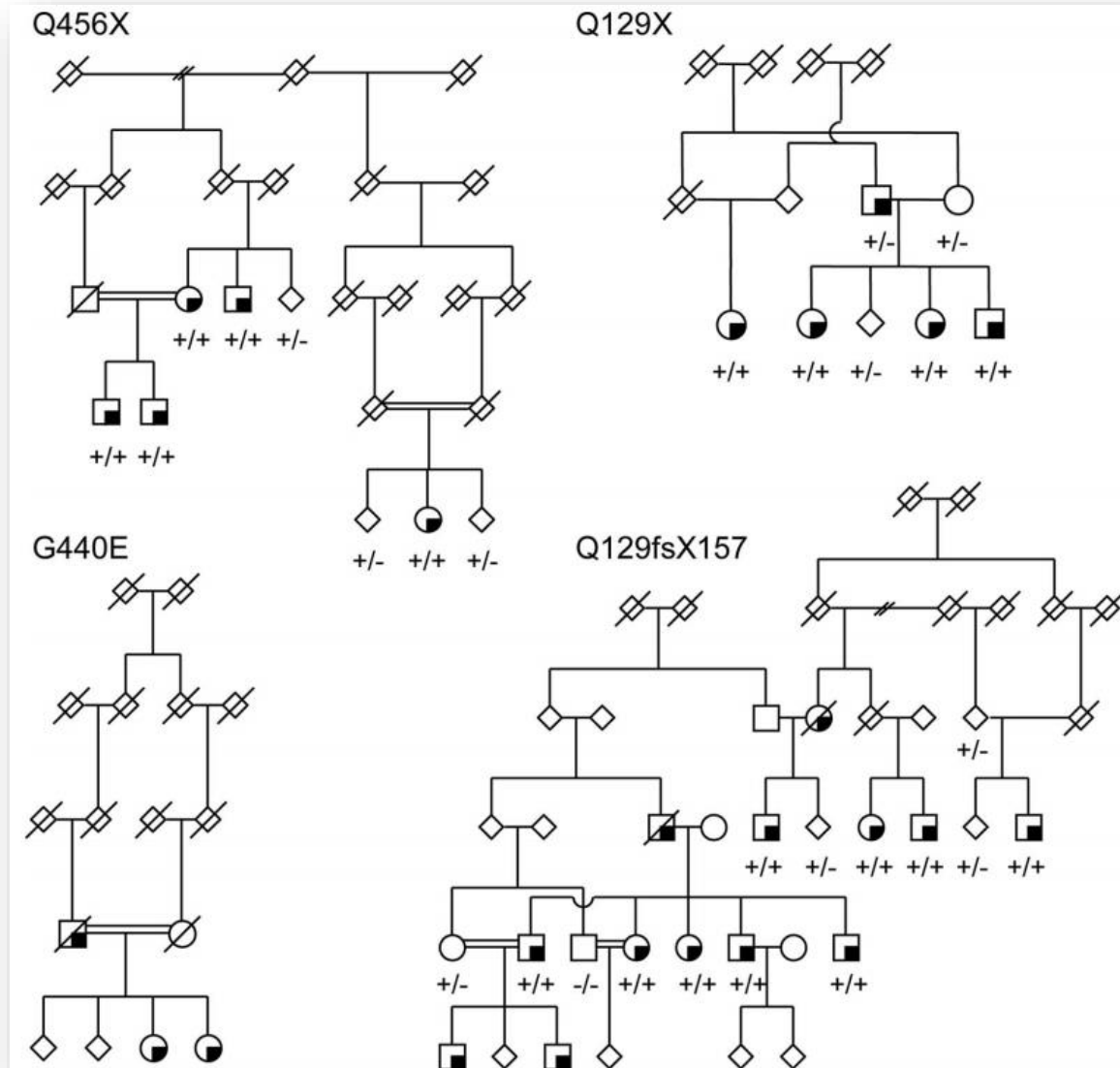
Table 1 Demographics of patients with genetically undefined, *LRRK2*, *PINK1* and *PRKN* Parkinson's disease

Variable	Genetically undefined PD (n = 107)	<i>LRRK2</i> (n = 73)	<i>PINK1</i> (n = 42)	<i>PRKN</i> (n = 9)
Age (years)	69 (27–96)	70 (38–91)	51 (25–76)	47 (32–79)
Age at onset (years)	60 (9–85)	60 (30–87)	35 (13–59)	32 (21–74)
Gender (Male) (n (%))	66 (62)	36 (49)	22 (52)	3 (33)
Disease duration (years)	6 (<1–49)	6 (1–28)	14 (<1–40)	11 (4–34)

The sample median (minimum-maximum) is given for age, age at onset and disease duration. *LRRK2*, leucine rich repeat kinase 2; *PINK1*, PTEN induced kinase 1; *PRKN*, parkin.

PINK1 mutation frequency = 18.2%
versus 1-2% EOPD in Western studies

PINK1 mutations and Parkinsonism



A comparative study of *LRRK2*, *PINK1* and genetically undefined familial Parkinson's disease

Kenya Nishioka,¹ Mounir Kefi,² Barbara Jasinska-Myga,^{1,3} Christian Wider,¹ Carles Vilariño-Güell,¹ Owen A Ross,¹ Michael G Heckman,⁴ Lefkos T Middleton,⁵ Lianna Ishihara-Paul,⁶ Rachel A Gibson,⁶ Rim Amouri,² Samia Ben Yahmed,² Samia Ben Sassi,² Mourad Zouari,² Ghada El Euch,² Matthew J Farrer,¹ Faycal Hentati²

Variable	Genetically undefined PD (n = 107)	<i>LRRK2</i> (n = 73)	<i>PINK1</i> (n = 42)
Age (years)	69 (27–96)	70 (38–91)	51 (25–76)
Age at onset (years)	60 (9–85)	60 (30–87)	35 (13–59)
Gender (Male) (n (%))	66 (62)	36 (49)	22 (52)
Disease duration (years)	6 (<1–49)	6 (1–28)	14 (<1–40)

Numerical feature	Median (minimum–maximum)			Single variable analysis p Value	Adjusting for gender, AAO, and DD p Value
	Genetically undefined (n = 107)	<i>LRRK2</i> (n = 73)	<i>PINK1</i> (n = 42)		
Hoehn and Yahr “on”	1 (0–5)	2 (0–5)	2 (1–4)	0.004	0.006
UPDRS III score “on”	6 (0–27)	10 (2–22)	8 (1–19)	0.002	0.003
UPDRS III score “off”	20 (3–80)	31 (8–80)	34 (2–67)	0.003	0.002
UPDRS total score “on”	27 (4–115)	41 (11–116)	44 (2–101)	0.004	0.002
LED	375 (0–1250)	375 (0–1125)	375 (0–1250)	0.51	0.25

A comparative study of *LRRK2*, *PINK1* and genetically undefined familial Parkinson's disease

Kenya Nishioka,¹ Mounir Kefi,² Barbara Jasinska-Myga,^{1,3} Christian Wider,¹ Carles Vilariño-Güell,¹ Owen A Ross,¹ Michael G Heckman,⁴ Lefkos T Middleton,⁵ Lianna Ishihara-Paul,⁶ Rachel A Gibson,⁶ Rim Amouri,² Samia Ben Yahmed,² Samia Ben Sassi,² Mourad Zouari,² Ghada El Euch,² Matthew J Farrer,¹ Faycal Hentati²

Categorical feature	Fraction (%)			Single variable analysis p Value	Adjusting for gender, AAO, and DD p Value
	Genetically undefined (n = 107)	LRRK2 (n = 73)	PINK1 (n = 42)		
Initial symptom (non-tremor)	14/106 (13%)	12/72 (17%)	16/41 (39%)	0.012	0.39
Drug induced dyskinesia	11/107 (10%)	18/73 (25%)	21/42 (50%)	<0.001	0.004
Drug induced dystonia	10/107 (10%)	6/72 (8%)	8/41 (20%)	0.13	N/A ψ
Drug induced motor fluctuations	10/106 (9%)	15/73 (21%)	14/42 (33%)	<0.001	0.042
Dopamine agonist use	57/104 (55%)	57/71 (80%)	36/41 (88%)	<0.001	<0.001
Tremor	101/107 (94%)	69/73 (95%)	33/42 (79%)	0.006	N/A ψ
Tremor—postural	70/101 (69%)	20/69 (29%)	11/33 (33%)	<0.001	<0.001
Tremor—resting	80/101 (79%)	68/69 (99%)	32/32 (100%)	0.006†	N/A ψ
Dystonia not related to treatment	8/107 (7%)	8/73 (11%)	6/42 (14%)	0.44	N/A ψ

PINK1 mutations in Zambian patients with PD

12 PD patients with early onset (< 50 years-old)
Sequencing of all PINK1 exons + MLPA for copy dosage analysis

Coding variants

Position	dbSNP accession N.	Variant allele frequency in dbSNP	Nucleotide change	Protein change	Homozygous PD carriers	Heterozygous PD carriers	Variant allele frequency in the patient cohort
PINK1							
Exon 1	novel		c.384C > A	p.Ile128Ile	0	1	0.042
Exon 6	rs45499398	0.034	c.1173T > C	p.Asp391Asp	0	1	0.042
Exon 7	rs115477764	0.034	c.1426G > A	p.Glu476Lys	0	2	0.083
Exon 8	rs1043424	0.200	c.1562A > C	p.Asn521Thr	0	7	0.292

No pathogenic mutations in PINK1

Assessing the prevalence of *PINK1* genetic variants in South African patients diagnosed with early- and late-onset Parkinson's disease

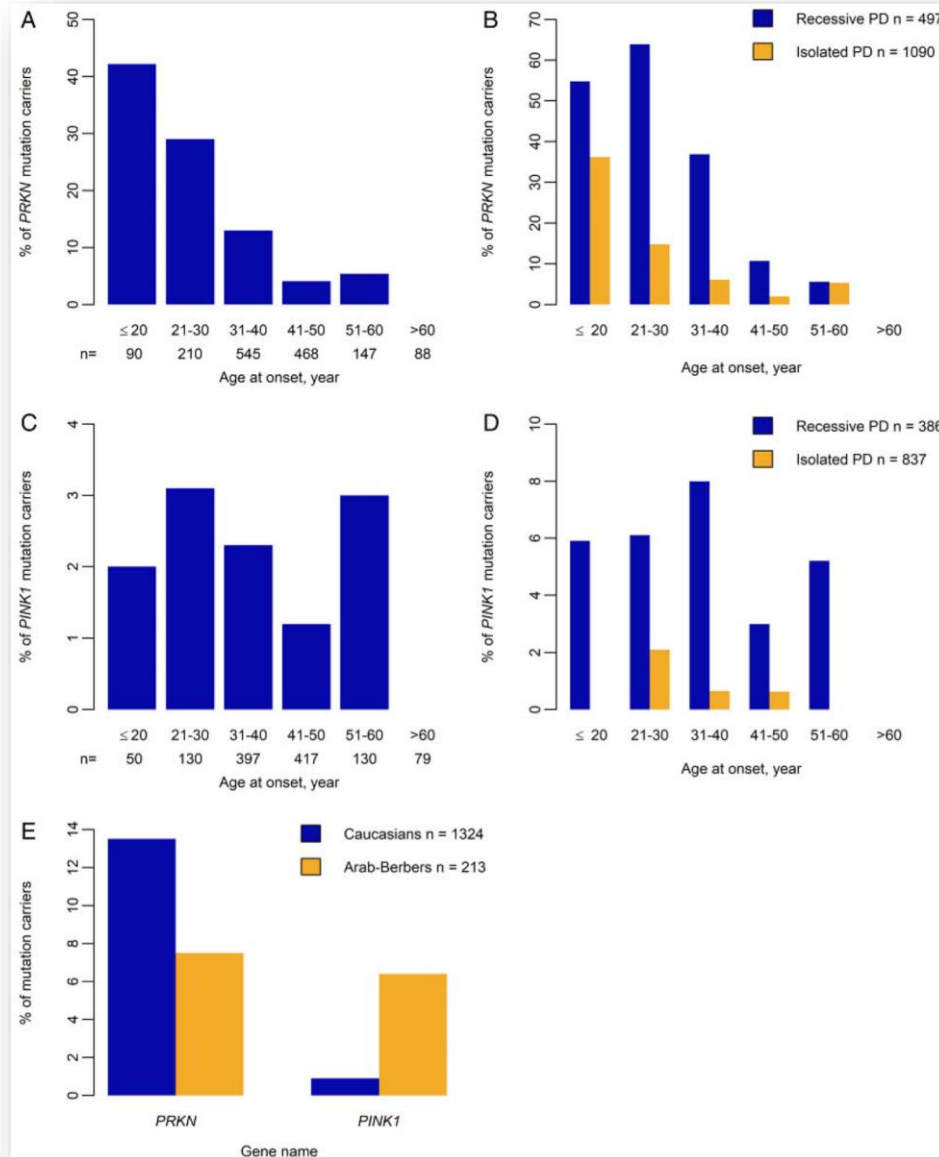
Rowena J. Keyser^a, Suzanne Lesage^{b,c,d}, Alexis Brice^{b,c,d}, Jonathan Carr^e, Soraya Bardien^{a,*}

154 PD patients with early onset and/or positive family history of PD
11.8% African origin
HRM and direct sequencing

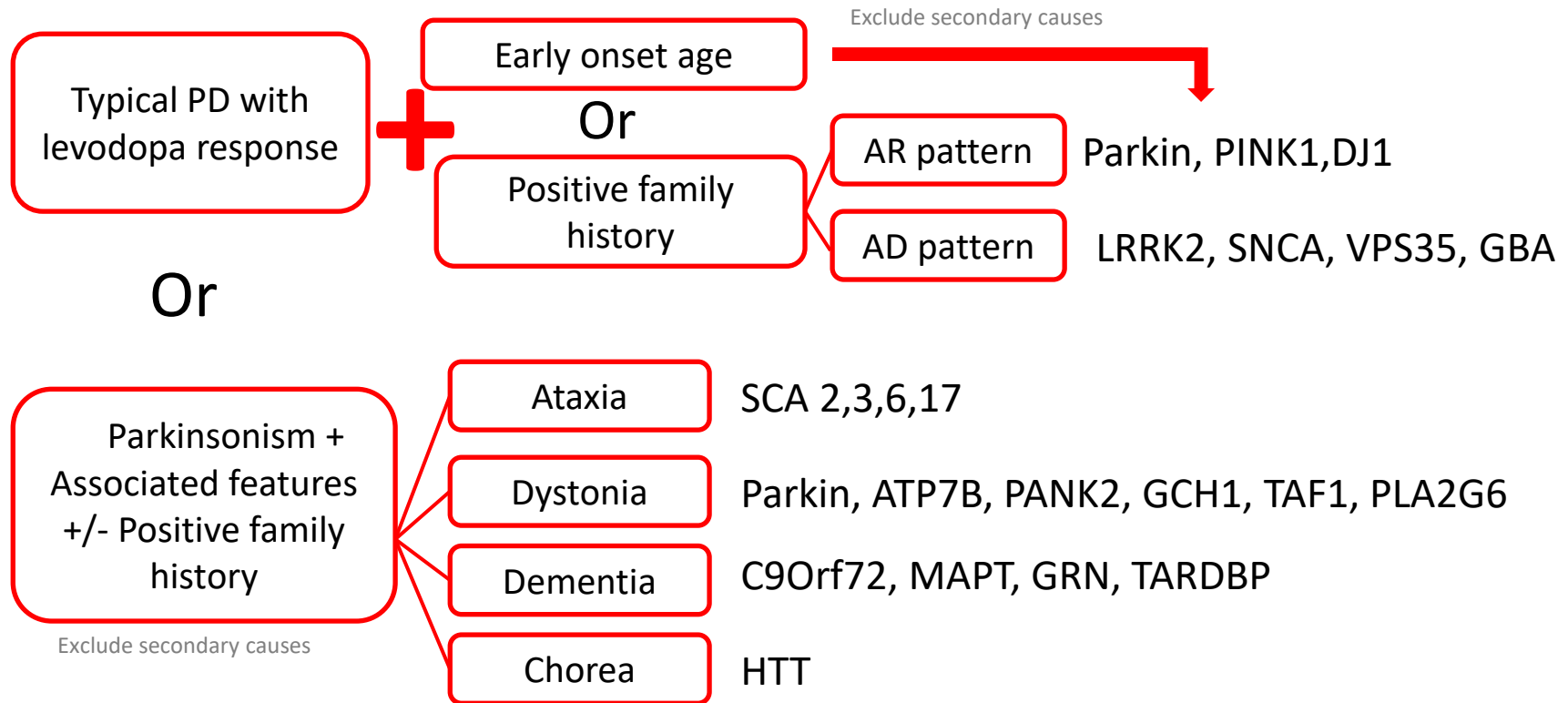
Known and putative mutations identified in *PINK1* in South African PD patients.

Exon	Variant	Zygosity	Number of patients/ ethnicity ^a	AAO (yrs)	Family history	Protein domain	Frequency in control chromosomes
3	Y258X (TAC- TAA)	Homozygous	1/Indian (68.10)	37	+	Kinase domain	0/130
4	P305A (CCT- GCT)	Heterozygous	1/Black (42.03)	30	+	Kinase domain	2/108 (1.9%)
7	E476K (GAG- AAG)	Heterozygous	1/Mixed ancestry (63.69)	48	—	Kinase domain	2/144 (1.4%)

Characterization of Recessive Parkinson Disease in a Large Multicenter Study



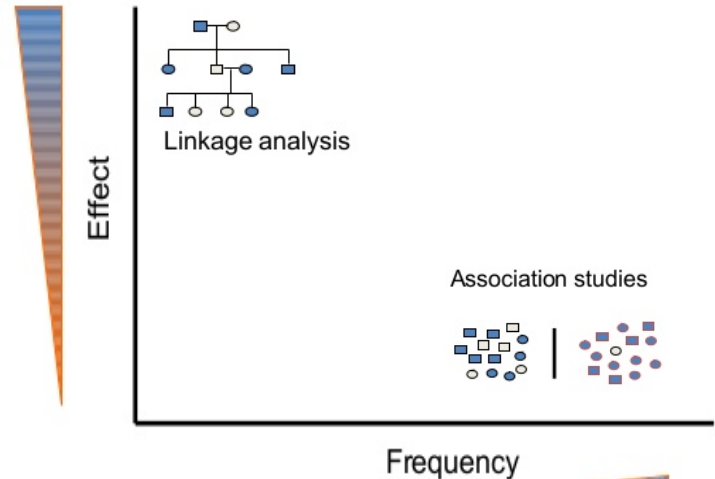
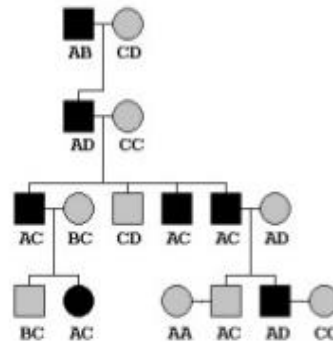
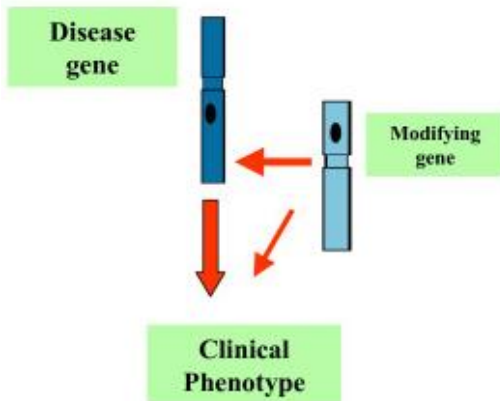
Genetic Testing for PD



PD Genetics : Mendelian vs. non-Mendelian inheritance

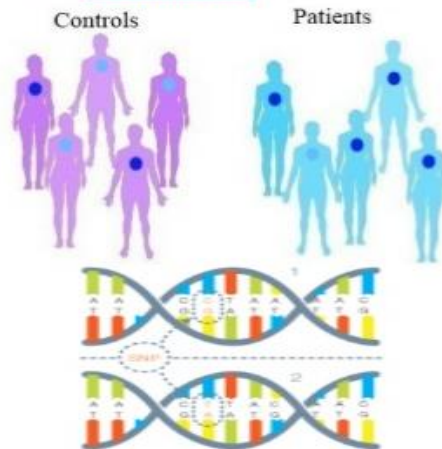
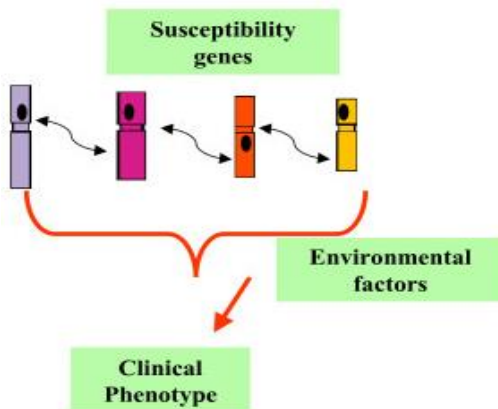
Mendelian or monogenic

- Linkage

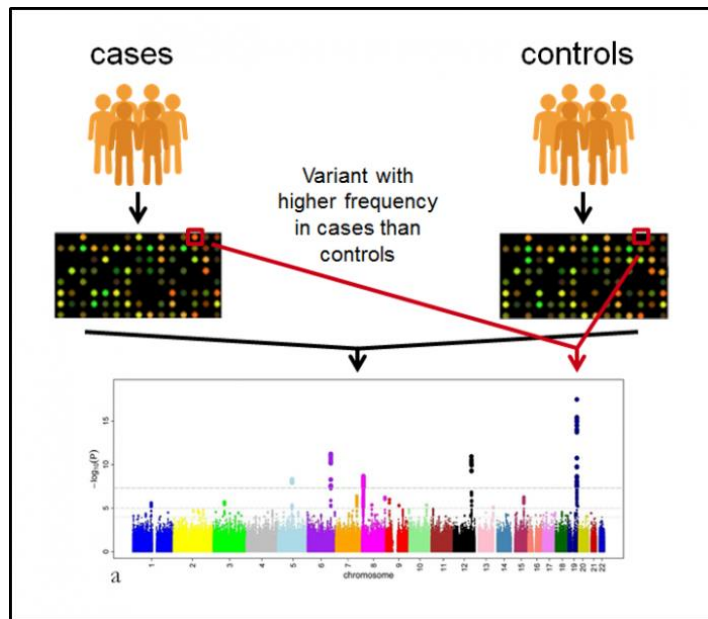


Complex or multifactorial

- Association

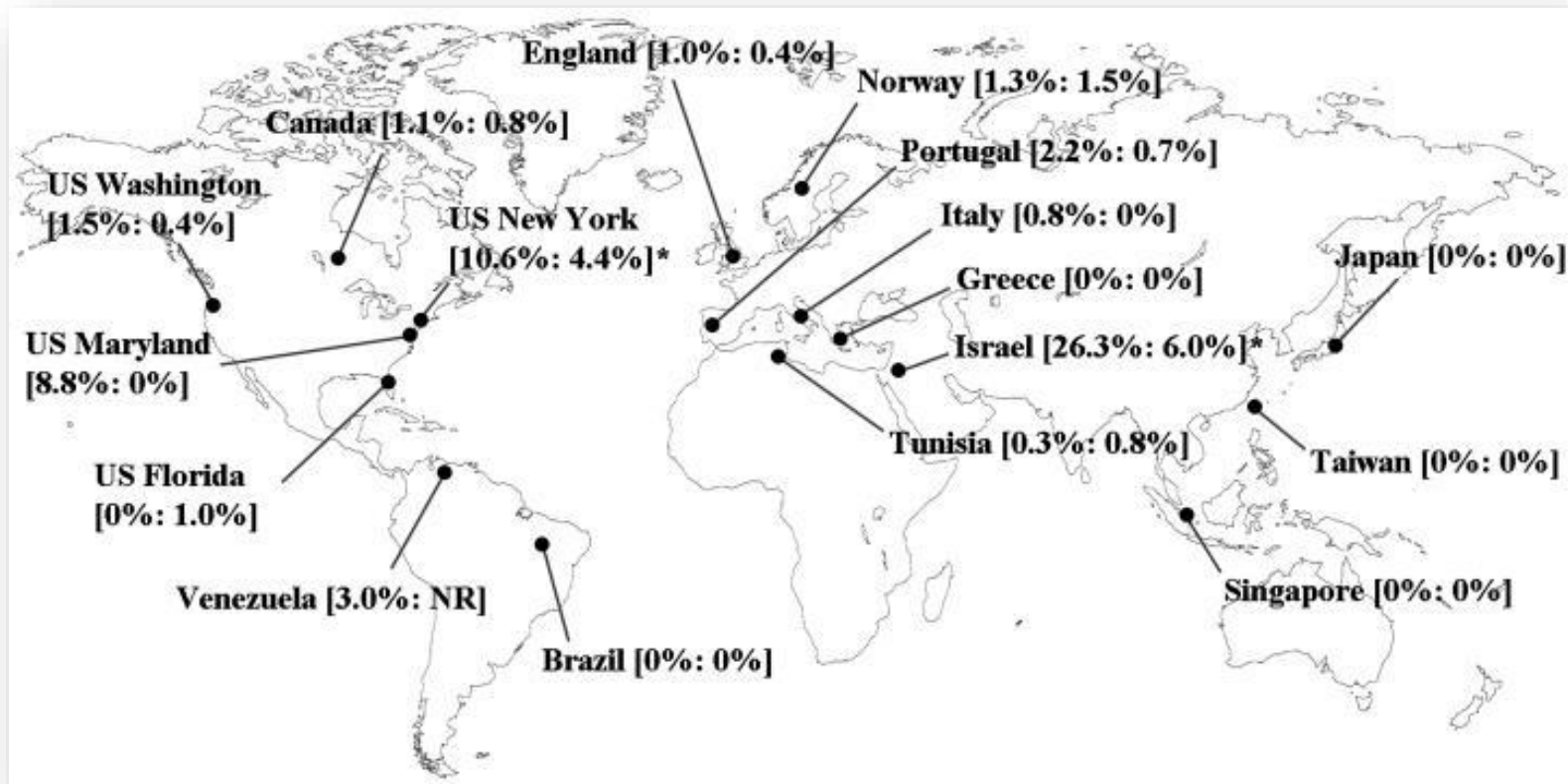


PD risk Loci

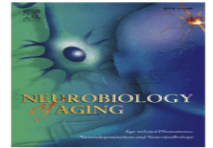


SNP	Chr	Base Pair	Nominated Gene	OR
rs35749011	1	155,135,036	<i>GBA/SYT11</i>	1.824
rs114138760	1	154,898,185	<i>GBA/SYT11</i>	1.586
rs823118	1	205,723,572	<i>RAB7L1/NUCKS1</i>	1.122
rs10797576	1	232,664,611	<i>SIPA1L2</i>	1.131
rs6430538	2	135,539,967	<i>ACMSD/TMEM163</i>	0.875
rs1474055	2	169,110,394	<i>STK39</i>	1.214
rs12637471	3	182,762,437	<i>MCCC1</i>	0.842
rs34311866	4	951,947	<i>TMEM175/GAK/DGKQ</i>	0.786
rs34884217	4	944,210	<i>TMEM175/GAK/DGKQ</i>	1.105
rs11724635	4	15,737,101	<i>BST1</i>	1.126
rs6812193	4	77,198,986	<i>FAM47E/SCARB2</i>	0.907
rs356182	4	90,626,111	<i>SNCA</i>	0.76
rs7681154	4	90,763,703	<i>SNCA</i>	0.934
rs9275326	6	32,666,660	<i>HLA-DQB1</i>	0.826
rs13201101	6	32,343,604	<i>HLA-DQB1</i>	1.217
rs199347	7	23,293,746	<i>GPNUMB</i>	1.11
rs591323	8	16,697,091	<i>FGF20</i>	0.916
rs117896735	10	121,536,327	<i>INPP5F</i>	1.624
rs329648	11	133,765,367	<i>MIR4697</i>	1.105
rs76904798	12	40,614,434	<i>LRRK2</i>	1.155
rs11060180	12	123,303,586	<i>CCDC62</i>	1.105
rs11158026	14	55,348,869	<i>GCH1</i>	0.904
rs2414739	15	61,994,134	<i>VPS13C</i>	1.113
rs14235	16	31,121,793	<i>BCKDK/STX1B</i>	1.103
rs11868035	17	17,715,101	<i>SREBF/RAI1</i>	0.939
rs17649553	17	43,994,648	<i>MAPT</i>	0.769
rs12456492	18	40,673,380	<i>RIT2</i>	0.904
rs8118008	20	3,168,166	<i>DDRKG1</i>	1.111

Glucocerebrosidase mutations are not a common risk factor for Parkinson disease in North Africa



Global distribution of GBA p.N370S mutant. Frequency of p.N370S in patients with PD followed by the frequency in control subjects.



Screening of the glucocerebrosidase (*GBA*) gene in South Africans of African ancestry with Parkinson's disease

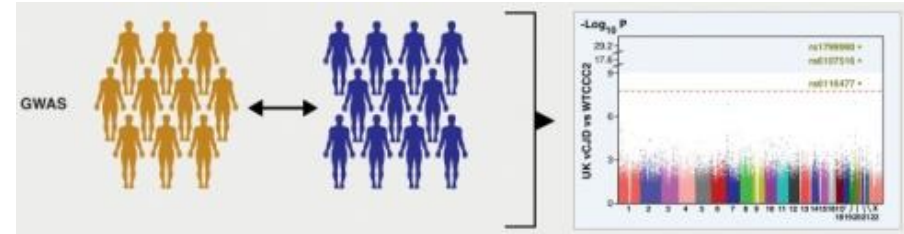
Amokelani C. Mahungu^a, David G. Anderson^b, Anastasia C. Rossouw^c,
Riaan van Coller^d, Jonathan A. Carr^e, Owen A. Ross^{f,g}, Soraya Bardien^{a,*}

Heterozygous coding variants identified in *GBA* in Parkinson's disease patients of African ancestry

Participant ID no.	Exon	^a Variant (traditional nomenclature)	^b Variant (HGVS nomenclature)	cDNA position	Codon change	rs number (dbSNP)	^c MAF from gnomAD (all)	MAF from gnomAD (African ancestry)	MAF from gnomAD (European ancestry; non-Finnish)
Nonsynonymous variants and indels									
43.59	2	p.K(-27)R	p.K13R	c.38A>G	AAG/AGG	rs150466109	0.007478	0.07687	0.0001629
12.170	2	p.K(-27)R	p.K13R						
10.313	2	p.K(-27)R	p.K13R						
10.314	2	p.K(-27)R	p.K13R						
11.895	2	p.K(-27)R	p.K13R						
11.910	2	p.K(-27)R	p.K13R						
11.835	3	p.T36del	p.T75del	c.222_224delTAC	GGTACC/GG-C	rs761621516	0.00006367	0.0004409	0.000
11.962	3	p.T36del	p.T75del						
12.486	5	p.R120W	p.R159W	c.475C>T	CGG/TGG	rs439898	0.00002124	0.0001203	0.00001552
94.69	5	p.R131L	p.R170L	c.509G>T	CGC/CTT	rs80356763	0.000003981	0.000	0.000
60.39	7	p.F216L	p.F255L	c.765C>T	TTC/TTA	Novel			
84.52	7	p.F216L	p.F255L						
12.172	7	p.F216L	p.F255L						
12.177	7	p.F216L	p.F255L						
12.179	7	p.F216L	p.F255L						
12.178	7 and 11	p.F216L and p.Q497*	p.F255L and p.Q536*	c.1606C>T	CAG/TAG	rs758806595	0.00002510	0.0002309	0.000
96.87	11	p.G478R	p.G517R	c.1549G>C	GCC/CGC	Novel			
Synonymous variants									
84.52	10	p.Q432Q	p.Q471Q	c.1413G>A	CAG/CAA	rs12747811	No data		

Common *GBA* variants, associated with PD risk were not found

LRRK2 exonic variants and susceptibility to Parkinson's disease



Common single variant associations with PD

SNP	Caucasian series				Asian series			Arab-Berber series		
	MA	MAF	OR (95% CI)	P-value	MAF	OR (95% CI)	P-value	MAF	OR (95% CI)	P-value
rs2256408 R50H	G	+	+	+	---	---	---	1.7%	2.05 (0.82, 5.14)	0.13
rs10878245 L153L	C*	39.6%	0.98 (0.91, 1.06)	0.57	31.2%	1.04 (0.88, 1.23)	0.65	47.1%	0.81 (0.55, 1.19)	0.28
rs34594498 A419V	T	+	+	+	1.9%	2.27 (1.35, 3.83)	0.0011	---	---	---
rs7308720 N551K	G	6.7%	0.88 (0.79, 0.98)	0.025	11.9%	0.73 (0.60, 0.89)	0.0017	8.0%	0.83 (0.49, 1.39)	0.47
rs10878307 I723V	G	7.4%	0.94 (0.84, 1.04)	0.23	1.1%	1.36 (0.74, 2.49)	0.32	9.0%	1.09 (0.68, 1.75)	0.71
rs34410987 P755L	T	---	---	---	0.6%	0.56 (0.27, 1.18)	0.13	---	---	---
rs58559150 Q923H	C	+	+	+	---	---	---	0.9%	0.62 (0.13, 2.99)	0.55
rs7966550 L953L	C	12.8%	0.98 (0.90, 1.07)	0.66	17.6%	0.80 (0.66, 0.95)	0.012	12.4%	0.92 (0.60, 1.41)	0.70
rs77018758 R1320S	T	---	---	---	1.2%	1.20 (0.69, 2.11)	0.51	---	---	---
rs17466213 I1371V	G	+	+	+	+	+	+	0.5%	4.45 (0.81, 24.56)	0.086
rs7133914 R1398H	A	6.6%	0.89 (0.80, 0.99)	0.034	11.5%	0.73 (0.59, 0.89)	0.0020	8.7%	1.00 (0.61, 1.64)	1.00
rs11175964 K1423K	A	6.6%	0.83 (0.74, 0.92)	0.0006	11.5%	0.75 (0.62, 0.92)	0.0064	5.4%	0.42 (0.21, 0.86)	0.011
rs35507033 R1514Q	A	0.9%	1.13 (0.85, 1.49)	0.41	---	---	---	+	+	+
rs33958906 P1542S	T	2.8%	0.90 (0.77, 1.06)	0.21	---	---	---	1.0%	2.27 (0.72, 7.13)	0.16
rs1427263 G1624G	C*	34.7%	1.06 (0.98, 1.14)	0.15	46.7%	0.92 (0.77, 1.11)	0.40	31.7%	0.96 (0.67, 1.39)	0.84
rs33949390 R1628P	C	+	+	+	1.2%	0.62 (0.36, 1.07)	0.087	---	---	---
rs11176013 K1637K	G*	45.0%	1.02 (0.94, 1.11)	0.60	44.6%	0.96 (0.80, 1.16)	0.68	46.0%	1.07 (0.70, 1.63)	0.76
rs35303786 M1646T	C	1.6%	1.43 (1.15, 1.78)	0.0012	---	---	---	+	+	+
rs11564148 S1647T	A	29.9%	0.93 (0.86, 1.00)	0.048	28.3%	0.97 (0.82, 1.15)	0.73	27.6%	0.81 (0.55, 1.19)	0.29
rs10878731 G1819G	C*	45.2%	1.06 (0.98, 1.15)	0.16	43.3%	0.99 (0.83, 1.19)	0.95	46.2%	1.07 (0.70, 1.64)	0.75
rs33995883 N2081D	G	2.6%	1.24 (1.05, 1.47)	0.013	+	+	+	4.7%	0.92 (0.49, 1.73)	0.79
rs10878405 E2108E	A	31.4%	0.96 (0.89, 1.03)	0.27	29.6%	1.01 (0.85, 1.20)	0.92	28.1%	0.75 (0.51, 1.10)	0.14
rs35658131 Y2189C	G	+	+	+	---	---	---	1.1%	4.48 (1.33, 15.09)	0.012
rs3477838348 G2385R	A	---	---	---	3.3%	1.73 (1.20, 2.49)	0.0026	---	---	---
rs33962975 G2385G	G	15.7%	0.97 (0.89, 1.06)	0.49	1.8%	0.96 (0.62, 1.49)	0.85	8.4%	1.14 (0.70, 1.83)	0.60
rs3761863 M2397T	C	34.4%	1.06 (0.98, 1.14)	0.17	43.9%	0.88 (0.73, 1.05)	0.16	39.8%	1.33 (0.85, 2.07)	0.21

Patient-Control Association Study of the LRRK2 Gene in South African Parkinson's Disease Patients

Case-control association results for the *LRRK2* variants that showed evidence for association in at least 1 South African ethnic group

SNP	Amino acid	MA	Afrikaner Caucasian				"non-Afrikaner" Caucasian				Mixed ancestry				Black African			
			MAF (%)		<i>P</i>		MAF (%)		<i>P</i>		MAF (%)		<i>P</i>		MAF (%)		<i>P</i>	
			PD	CON	Add	Dom	PD	CON	Add	Dom	PD	CON	Add	Dom	PD	CON	Add	Dom
rs10878245	L153L	T	37.1	39.2	0.691	0.838	35.5	47.3	0.019	0.111	65.7	52.4	0.064	0.244	75.0	69.7	0.527	0.795
rs33958906	P1542S	T	3.2	2.7	0.799	0.799	1.1	6.4	0.013	0.018	0	1.2	0.238	0.238	—	—		
rs11176013	K1637K	A	45.2	51.1	0.317	0.703	38.5	50.5	0.023	0.205	52.9	39.4	0.053	0.070	50.0	43.4	0.476	0.289
rs11564148	S1647T	A	24.6	25.3	0.890	0.923	29.3	29.7	0.932	0.890	28.6	25.9	0.648	0.748	0	13.4	0.004	0.004
rs10878371	G1819G	T	43.7	51.6	0.170	0.479	39.5	50	0.039	0.207	52.9	40.4	0.077	0.076	50.0	43.9	0.505	0.314
rs34637584	G2019S	A	—	—			1.7	0	0.032	0.032	1.4	0	0.114	0.114	—	—		
rs10878405	E2108E	A	36.1	24.7	0.036	0.022	32.7	32.8	0.988	0.826	17.6	26.5	0.133	0.139	0	10.6	0.010	0.010
rs33962975	G2385G	G	7.9	12.5	0.182	0.219	8.1	14.1	0.056	0.070	18.6	8.4	0.026	0.042	3.1	6.1	0.454	0.454

Common LRRK2 variants, associated with PD risk, were not found

The role of SNCA and MAPT in Parkinson disease and LRRK2 parkinsonism in the Tunisian Arab-Berber population

- SNPs in SNCA and MAPT assessed using Affymetrix 500K arrays.

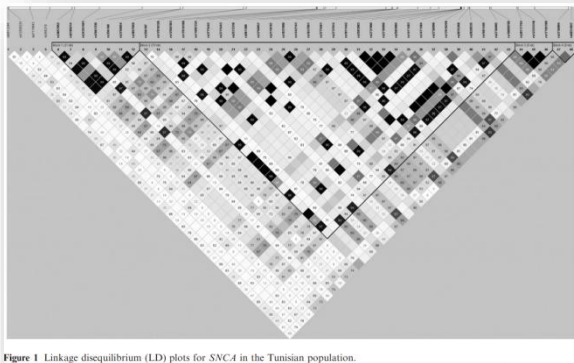


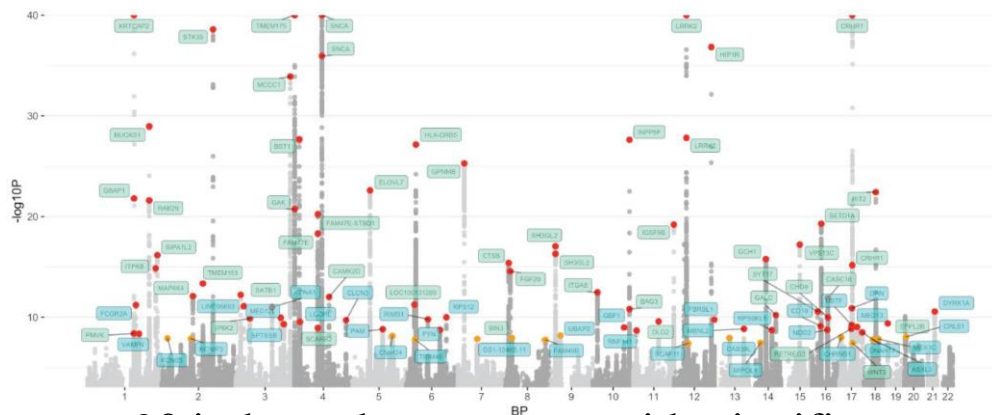
Table 1 Significant association shown for *SNCA* in idiopathic PD and *LRRK2* parkinsonism. A Bonferroni corrected $P < 2.3 \times 10^{-3}$ is considered significant for the number of markers examined. LD block 1 is spanning 31 kb and the 3' centromeric end of the gene. LD block 2 is at the 5' telomeric end of the gene

Gene	Hg19 position	iPD association (<i>P</i> value)	OR (95% CI)	<i>LRRK2</i> parkinsonism (<i>P</i> value)	OR (95% CI)
<i>SNCA</i>					
rs356219	Chr4: 90637351	6.0×10^{-4}	1.65 (1.14–2.37)	0.18	0.93 (0.58–1.51)
rs7661330	Chr4: 90663670	1.40×10^{-4}	0.64 (0.45–0.93)	0.77	0.91 (0.58–1.44)
rs356168	Chr4: 90674431	8.95×10^{-4}	1.64 (1.14–2.36)	0.49	0.94 (0.58–1.52)
rs3756054	Chr4: 90674451	1.67×10^{-4}	1.67 (1.16–2.4)	0.70	0.97 (0.6–1.57)
rs3857059	Chr4: 90675238	8.71×10^{-4}	1.37 (0.67–2.83)	0.80	1.1 (0.39–3.07)
rs17016168	Chr4: 90713259	5.10×10^{-4}	1.68 (1.13–2.49)	0.24	0.85 (0.5–1.44)
rs3775443	Chr4: 90715674	3.01×10^{-4}	1.71 (1.14–2.55)	0.22	0.81 (0.48–1.38)
rs3756057	Chr4: 90734426	1.96×10^{-4}	1.68 (1.13–2.5)	0.15	0.85 (0.5–1.44)
rs3775461	Chr4: 90741803	2.66×10^{-4}	2.04 (1.22–3.4)	0.22	0.75 (0.38–1.5)
rs17016259	Chr4: 90754955	9.24×10^{-4}	1.66 (1.11–2.47)	0.24	0.85 (0.5–1.45)
rs2035268	Chr4: 90756077	4.49×10^{-4}	1.65 (1.14–2.37)	0.22	0.93 (0.58–1.51)

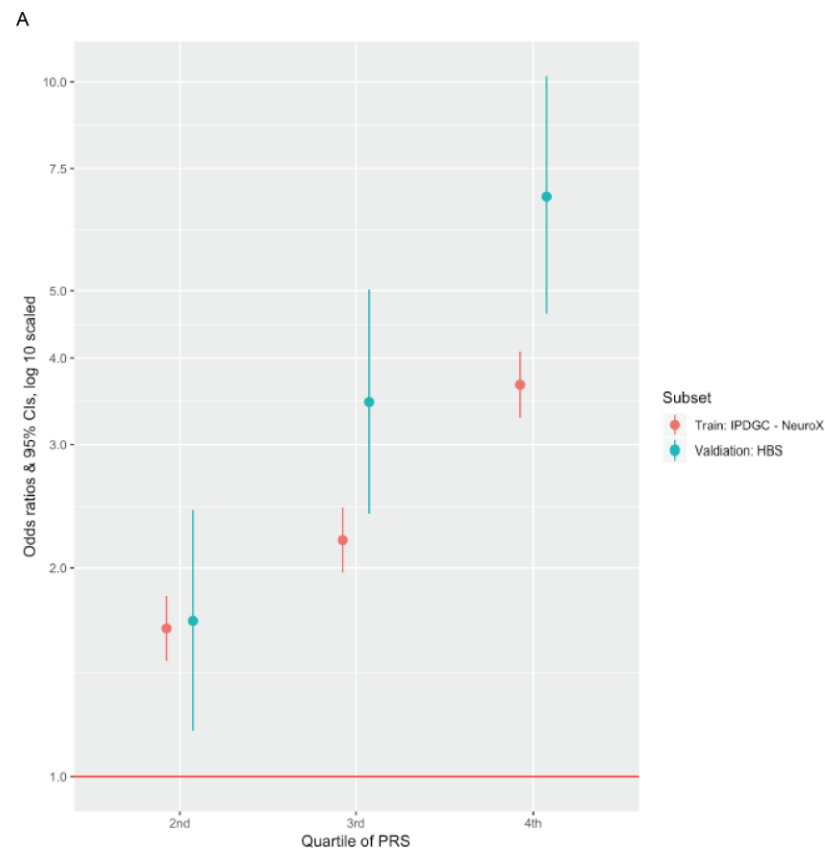
MAPT variants were not associated with susceptibility to PD
Several variants in SNCA seemed to increase the risk for sporadic PD

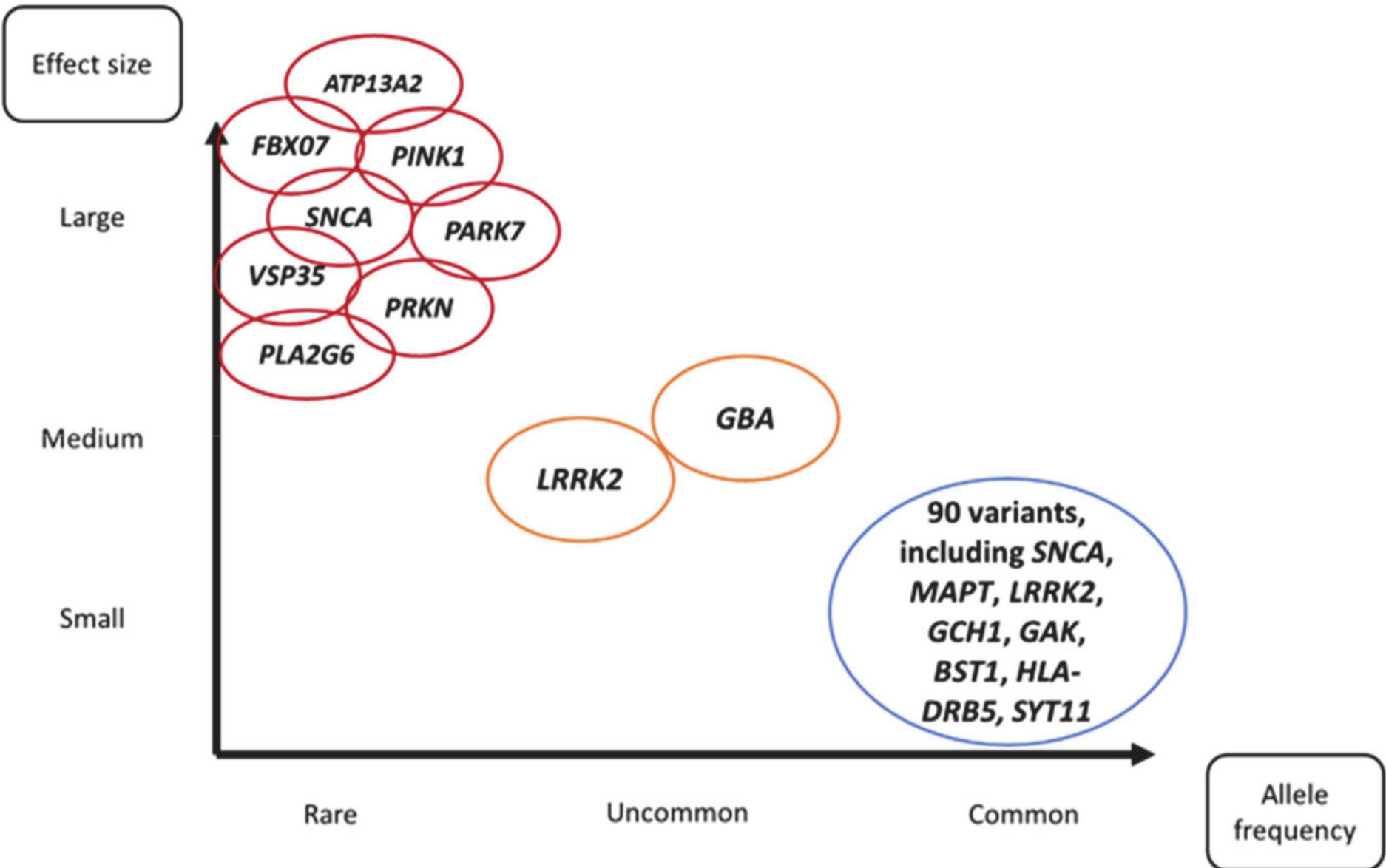
Polygenic risk Score

Meta-GWAS : 7.8M SNPs in 37.7K PD cases, 18.6K cases having a first degree relative with PD and 1.4M controls.

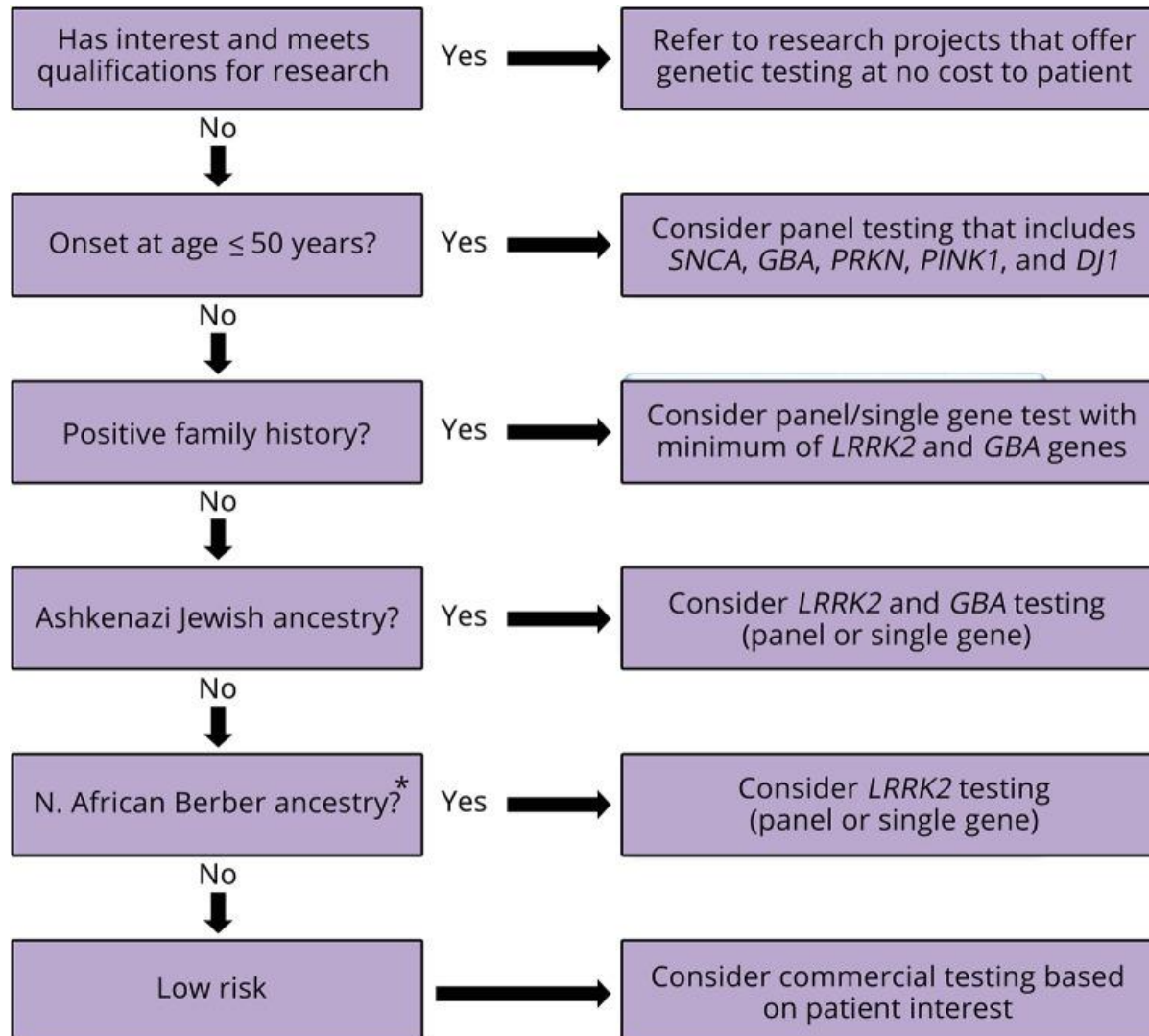


90 independent genome-wide significant association signals

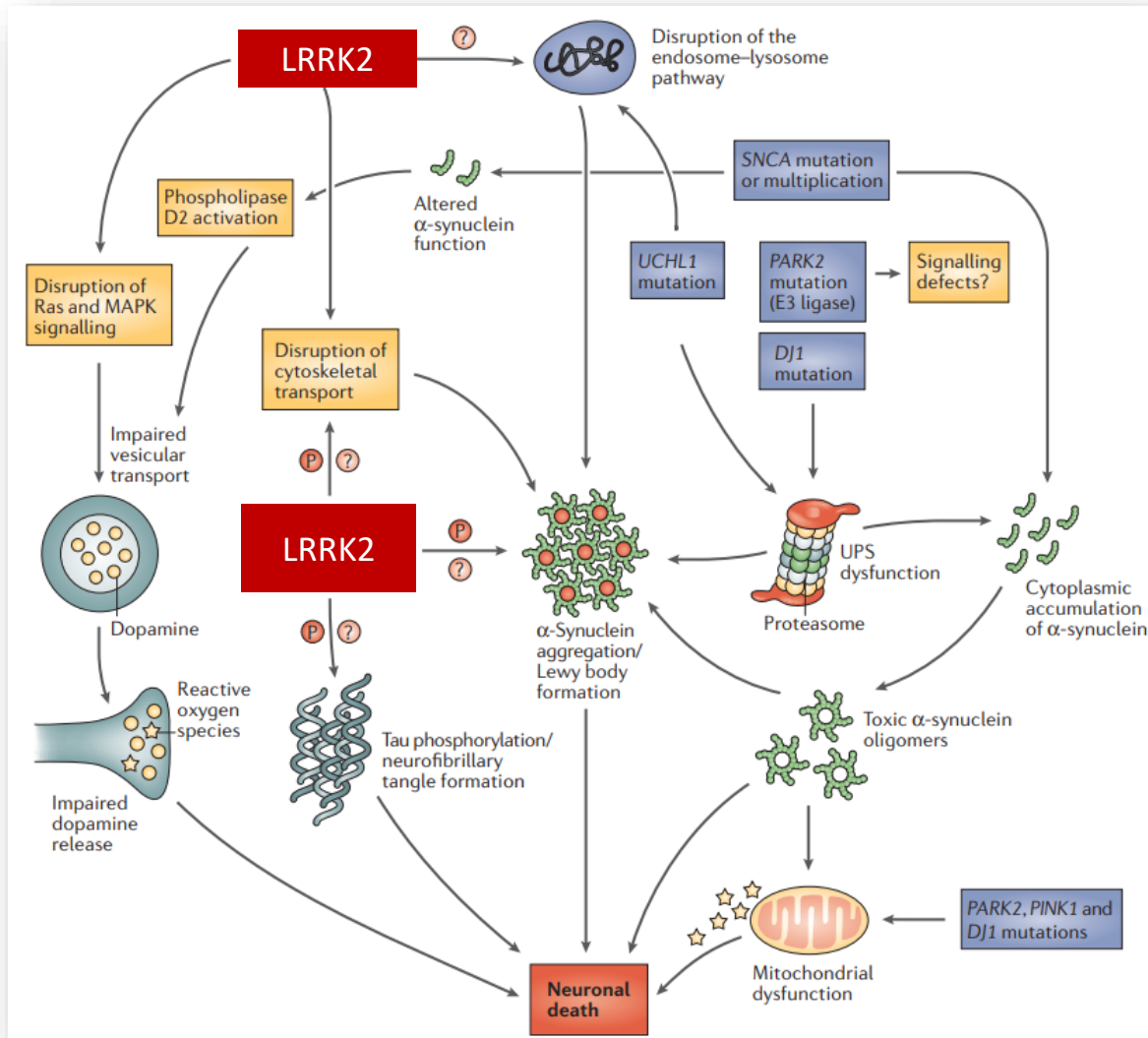




Genetic Testing for PD

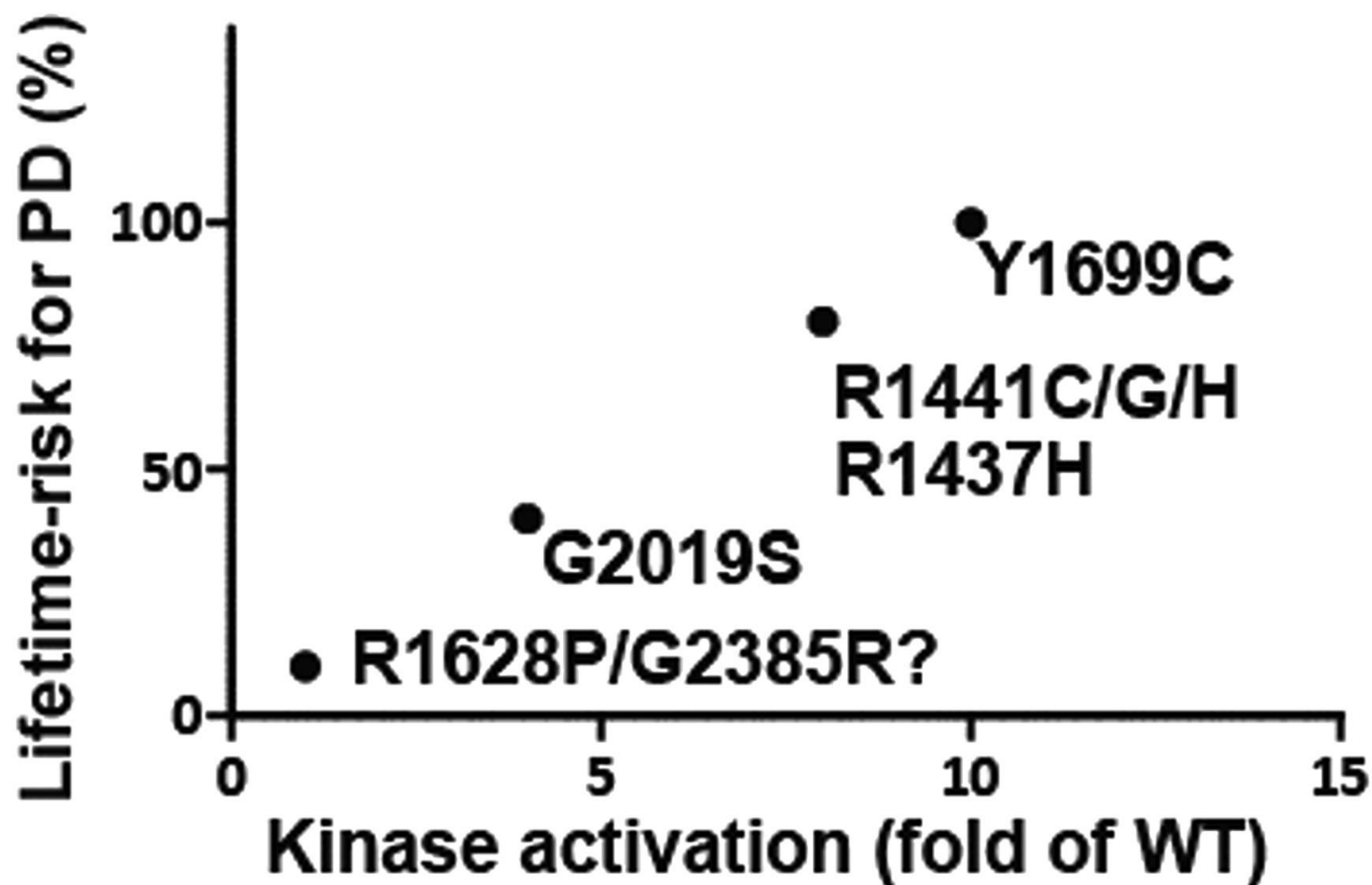


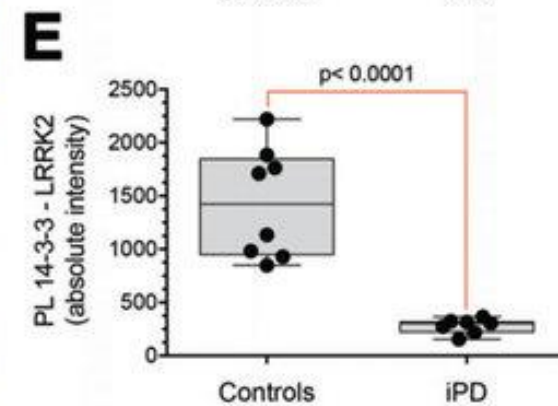
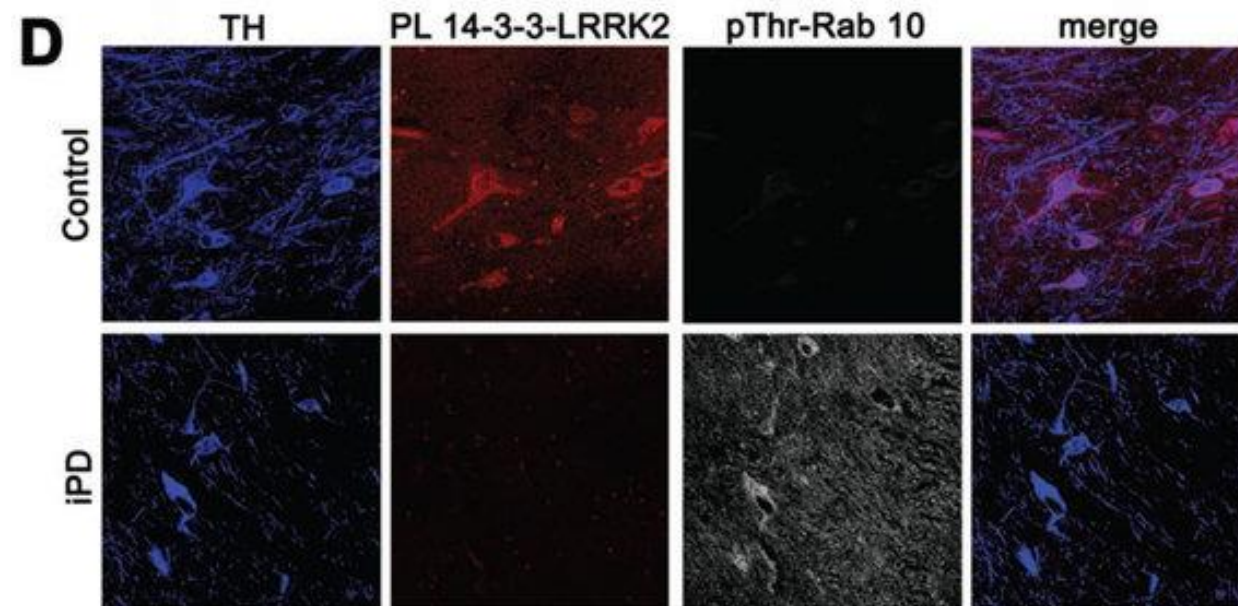
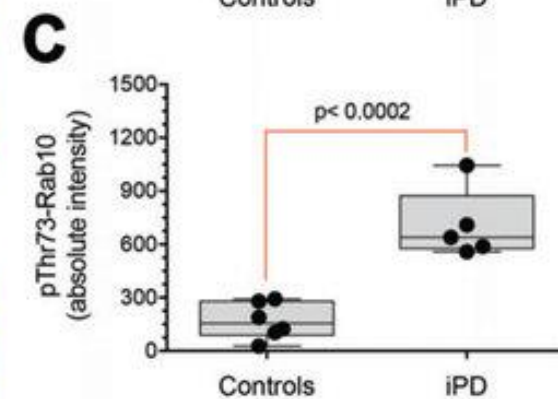
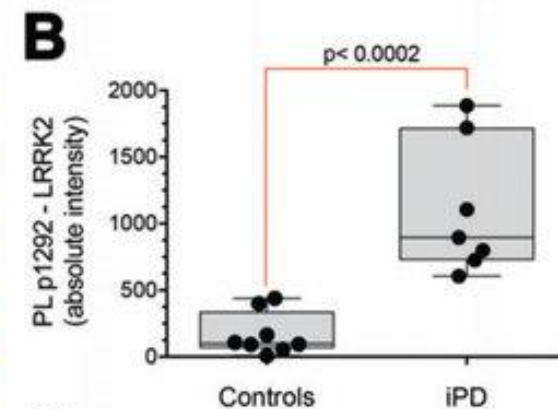
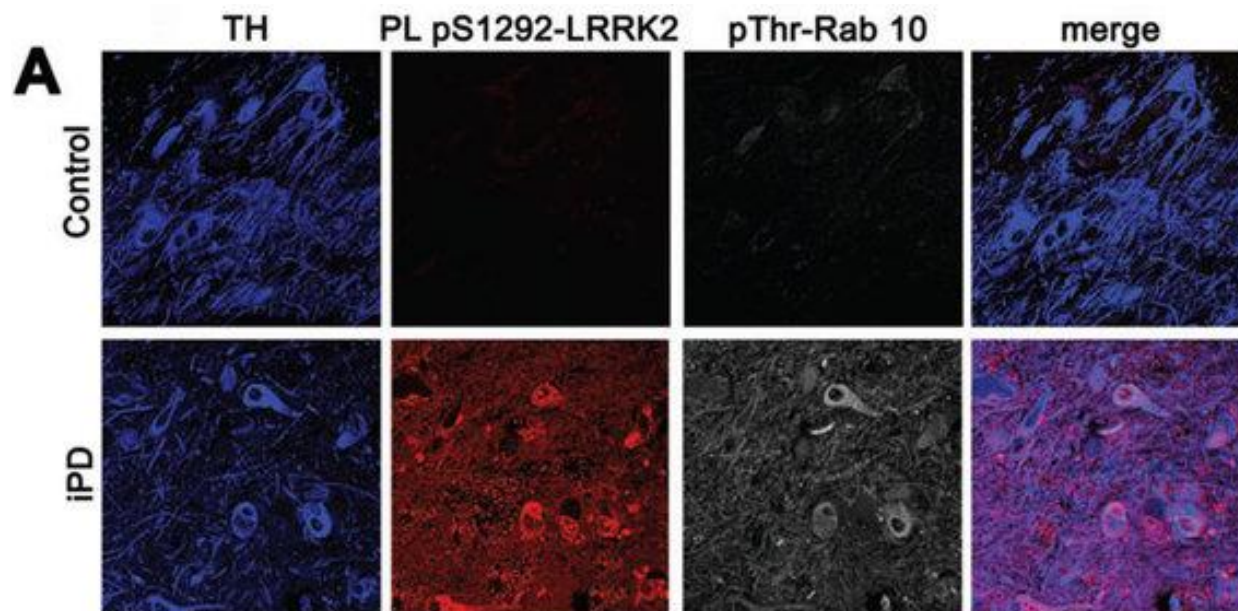
Pathways to Parkinson's disease



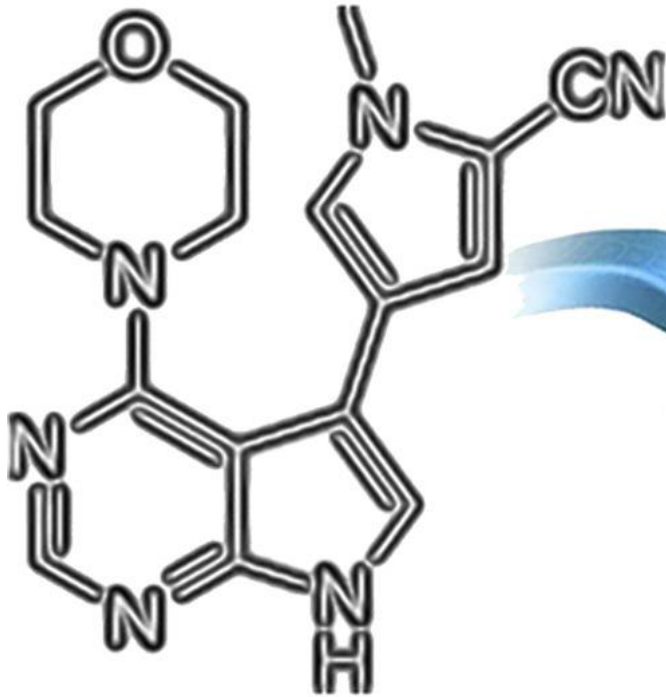
LRRK2 Kinase

Activation Hypothesis

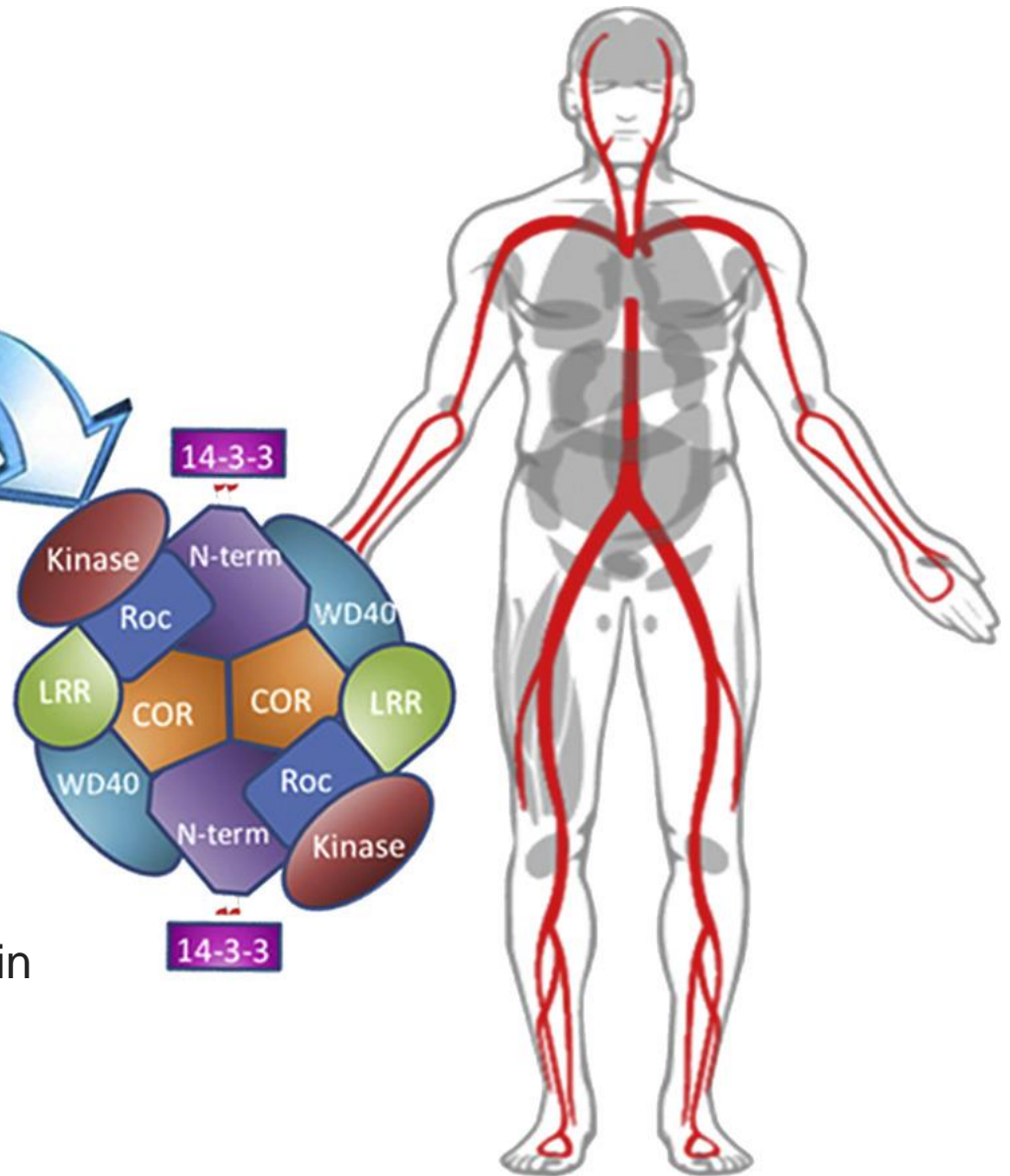




LRRK2 Inhibitors



- Highly specific towards LRRK2
- Potent
- Permeable though the blood–brain barrier
- Safe in prolonged use
- Easily administered



Clinical Trials

LRRK2				
Compound	DNL201	DNL151	BIIB122/DNL151	BIIB094
Sponsor	Denali	Denali	Biogen/Denali	Biogen
Mechanism	LRRK2 inhibition	LRRK2 inhibition	LRRK2 inhibition	Antisense oligonucleotide (ASO)
Status	Completed	Completed	Ongoing, estimated completion end of 2031	Ongoing, estimated completion end of 2022
Phase	Phase 1b	Phase 1b	Phase 2/3	Phase 1
Design	Multicenter, randomized, placebo-controlled	Multicenter	International, multicenter, placebo-controlled	International, multicenter, placebo-controlled
Total N of patients	29	34	400	62
LRRK2-PD	✓	✓	✓	✓
Idiopathic PD	✓	✓	✓	✓
Age	30–75		30-80	35–80
Duration	28 days	28 days	180 weeks	n.d.
Doses tested	Low/high	Three doses	Single dose	Single- and multiple-ascending-dose

Thank you

