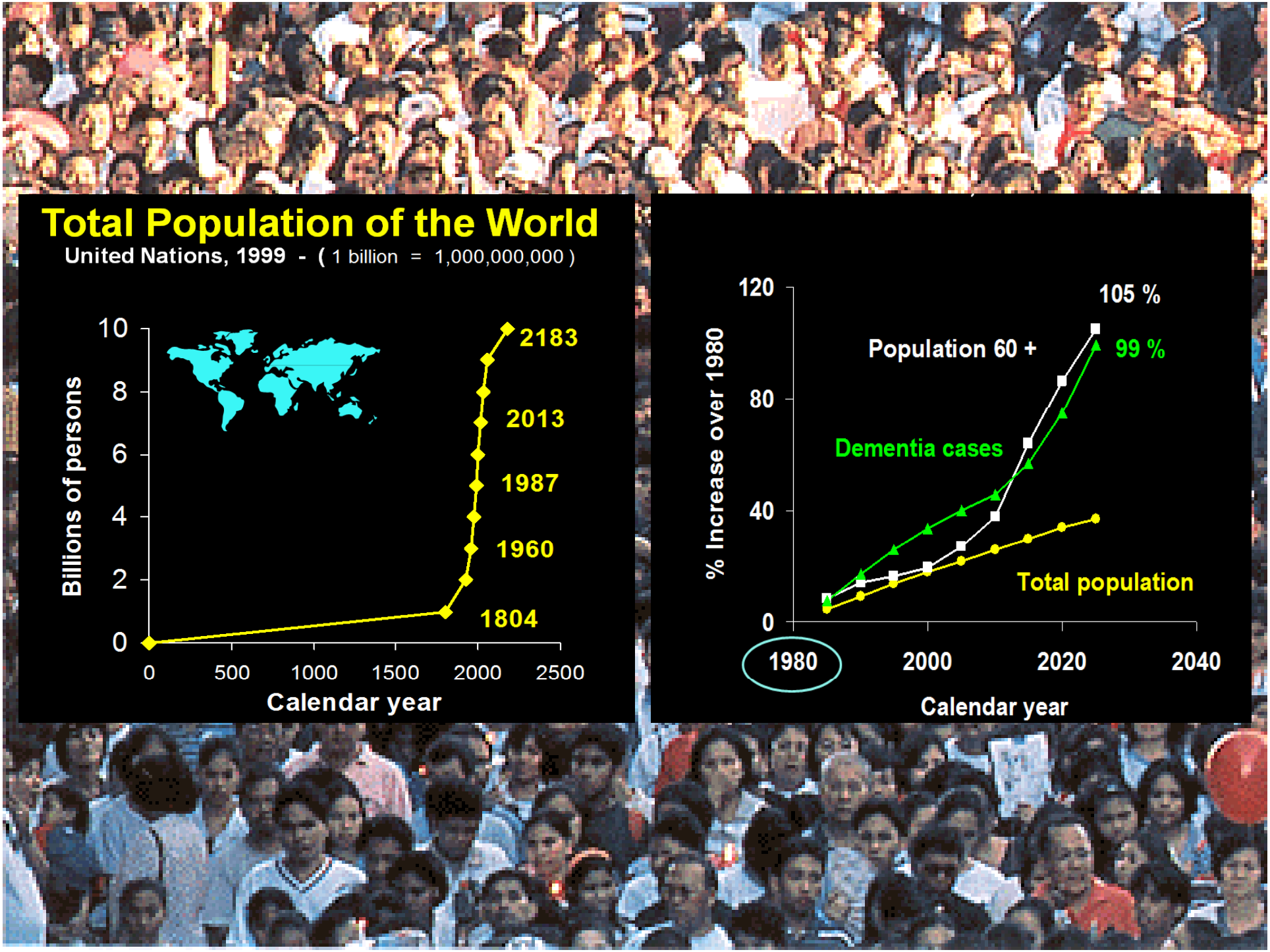
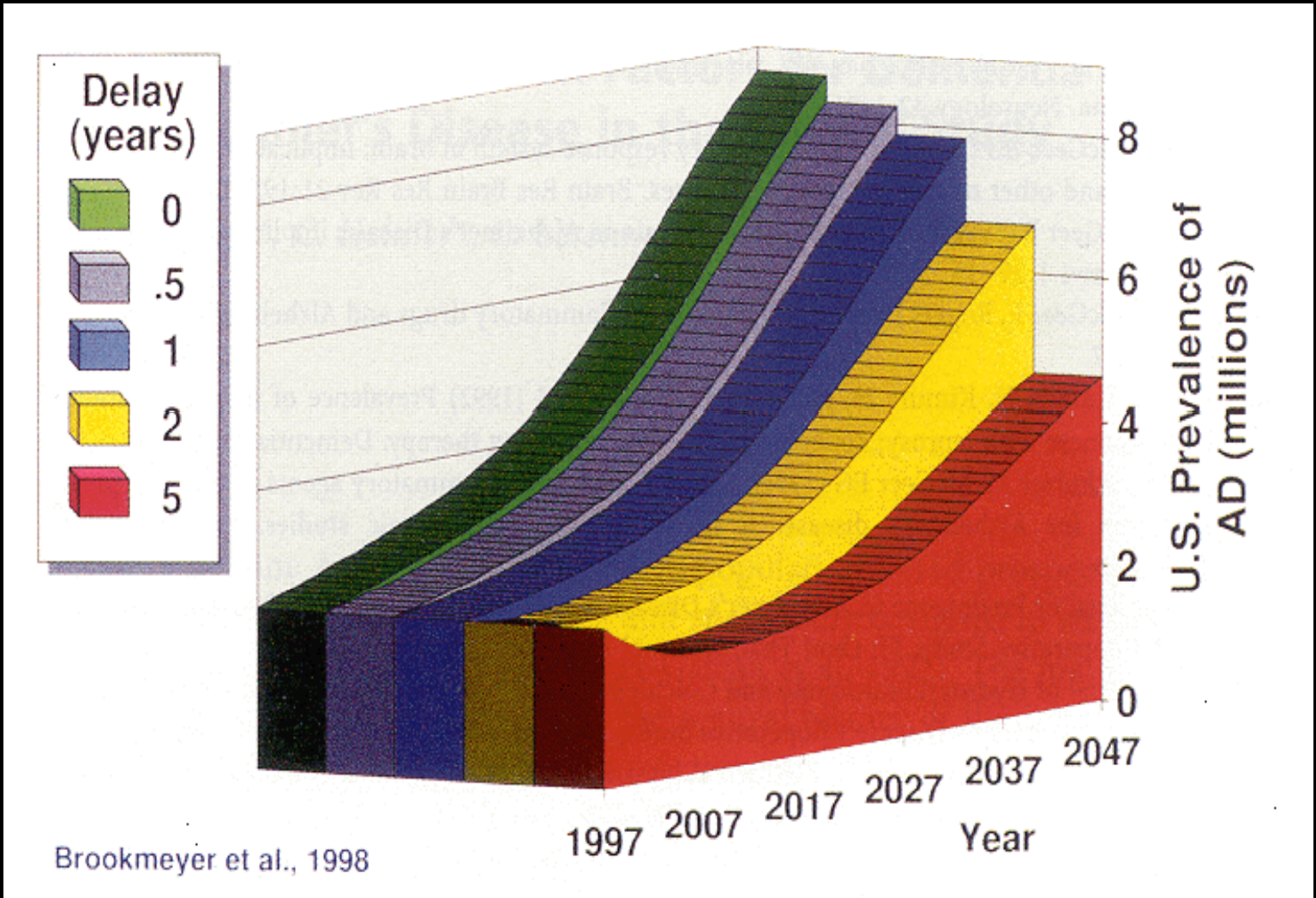
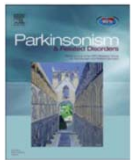

Total Population of the World
United Nations, 1999 - (1 billion = 1,000,000,000)
Billions of persons
10
8
6
4
2
0
0
500
1000
1500
2000
2500
Calendar year
2183
2013
1987
1960
1804
% Increase over 1980
120
80
40
0
1980
2000
2020
2040
Calendar year
105 %
Population 60 +
99 %
Dementia cases
Total population

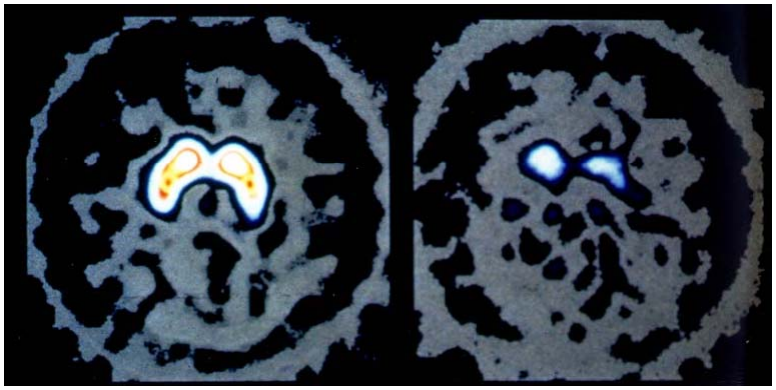
Impact of Delaying Onset

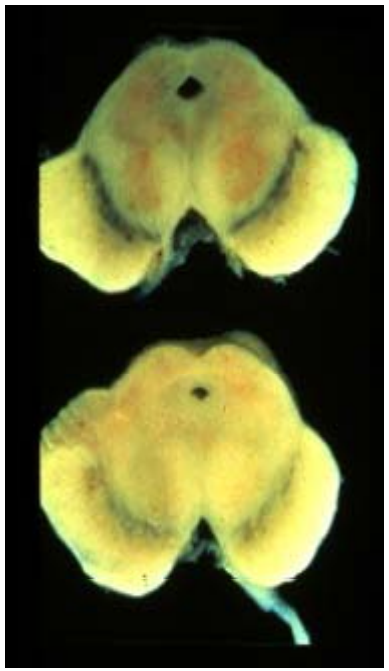
Brookmayer et al., 1998

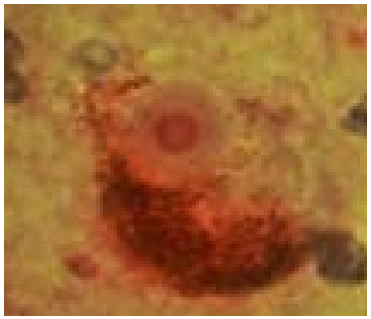


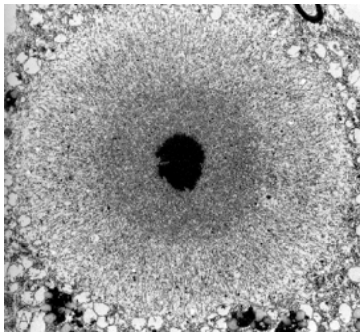
Burden of Illness in Parkinson's Disease











Complications	PD patients	Controls
Neuropsychiatric disorders		
Dementia	3,115 (15.6)	692 (3.5)
Delirium	1,545 (7.7)	342 (1.7)
Depression	2,521 (12.6)	953 (4.8)
Hallucinations	177 (0.9)	22 (0.1)
Any of the above	5,572 (27.8)	1,760 (8.8)
Falls and injuries		
Falls	786 (3.9)	265 (1.3)
Fractures	2,586 (12.9)	1,272 (6.4)
Sprains	1,935 (9.7)	1,650 (8.2)
Contusions	1,493 (7.5)	670 (3.3)
Lacerations	1,787 (8.9)	901 (4.5)
Any of the above	5,761 (28.8)	3,670 (18.3)
Sleep disorders		
Insomnia/parasomnias	577 (2.9)	334 (1.7)
Restless legs syndrome	149 (0.7)	15 (0.1)
Excessive sleepiness	221 (1.1)	105 (0.5)
Any of the above	843 (4.2)	428 (2.1)
Autonomic dysfunction		
Constipation	1,504 (7.5)	649 (3.2)
Urinary problems	1,775 (8.9)	741 (3.7)
Sexual problems	226 (1.1)	201 (1.0)
Orthostatic hypotension	808 (4.0)	238 (1.2)
Dysphasia	422 (2.1)	149 (0.7)
Dysphagia	2,665 (13.3)	702 (3.5)
Seborrhea/blepharitis	507 (2.5)	339 (1.7)
Any of the above	6,185 (30.9)	2,650 (13.2)

Values are expressed as n (%).

The economic impact of Parkinson's disease

Movement Disorders

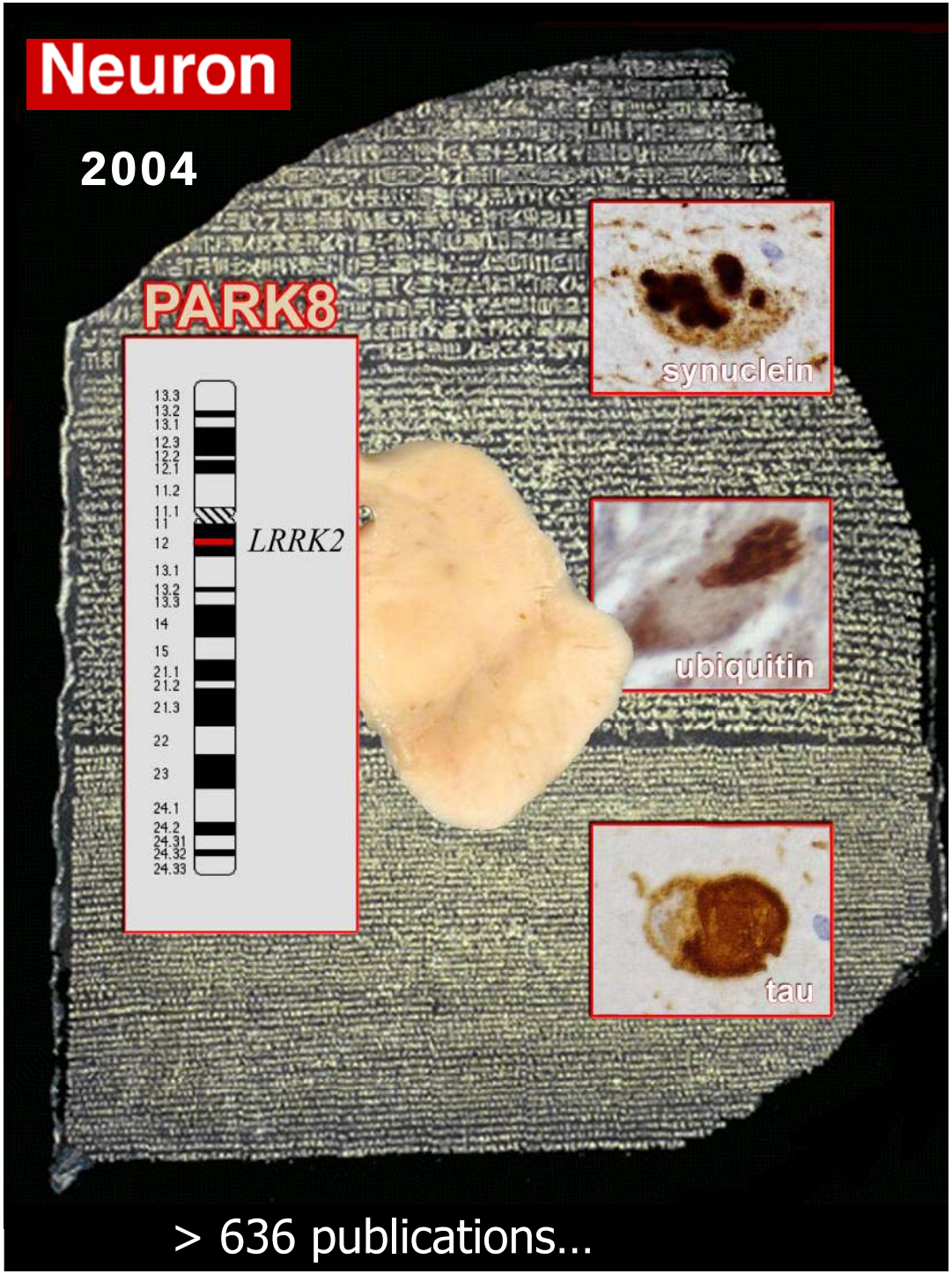
Country	Year	Citation	Number of PD patients	Study period	Data collection	Method of attributing cost to PD	Annual direct cost ($)	Comments
Canada	1993–1999	5	15,306	6 yr	Insurance claims	Control group	1,750	Physician and prescription drug costs only
Finland	1998	7	258	1 yr	Chart review and survey	Total cost	5,949	Excluded patients using COMT inhibitors
France	1996	8	294	6 mo	Survey	Total cost	6,769	Excluded newly diagnosed patients; oversampled severe motor fluctuations
Germany	1995	3	40	3 mo	Survey	Total cost	17,560	Included drug treated patients only; sampled equal number from each Hoehn-Yahr stage
Sweden	2000	6	127	1 yr	Chart review and survey	Individual PD services	8,374	Method for identifying PD-related services not specified
UK	1998	4	432	1 yr	Survey	Total cost	11,154	Random sample of GP practices
USA	1987	10	43	1 yr	Survey	Control group	12,397	Excludes institutionalized patients
USA	1994	11	109	1 yr	Survey	Total cost	7,371	Less than 10% were institutionalized
USA	1995–1998	9	455	NR	Insurance claims	Individual PD services	2,706	Method for identifying PD-related services not specified
USA	1999–2002	—	20,016	3 yr	Insurance claims	Control group	10,349	Adjusted for differences in comorbidity between PD cases and controls

PD, Parkinson's disease; COMT, catechol-*O*-methyltransferase; GP, general practitioner; NR, not recorded.

Direct+ indirect costs in UK = £0.45- 3.3B, USA=$23B

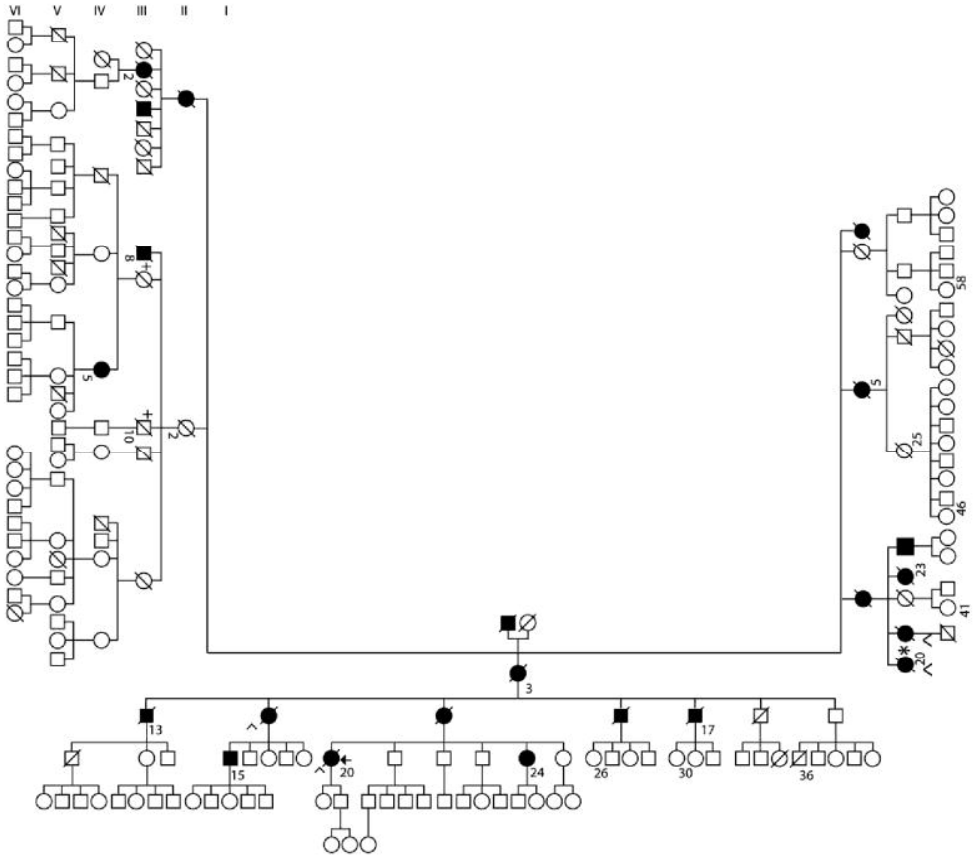
Leucine-rich repeat kinase 2

→ Neuroprotective therapeutics

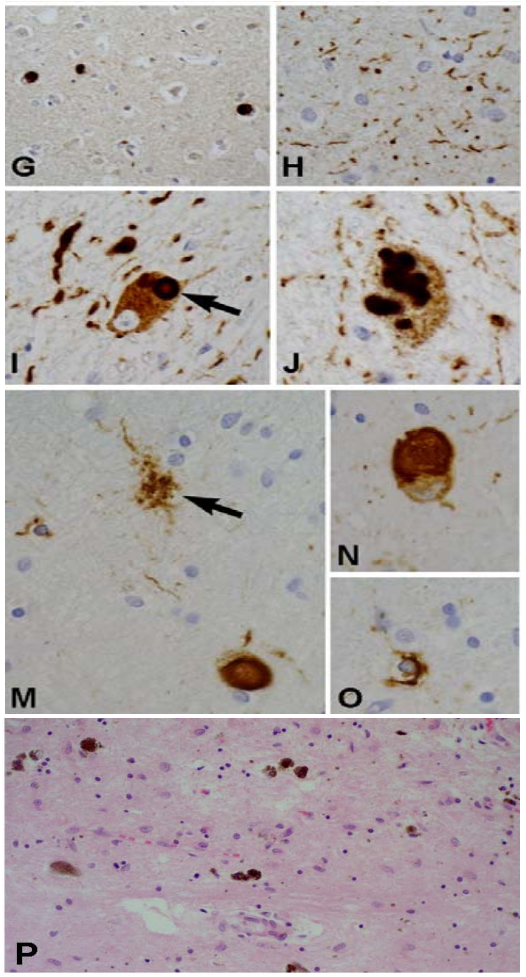


Neuron **2004**

Family D
(Western Nebraska)



- XIX century English
- Clinical PD, mean onset ~65 yrs, 13 yrs duration
- Plus gaze palsy at 83 yrs, 5 yrs after onset (n=1)



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chr12:38918058 rs10878245 L153L
chr12:38918147 rs35517158
chr12:38920612 LRRK2_A211V
chr12:38923625 rs28365216
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Chr12:38931430 rs72546336
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chr12:38943967 rs7308720 N551K
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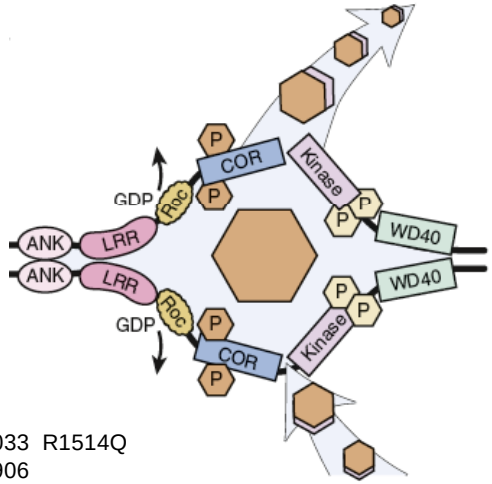
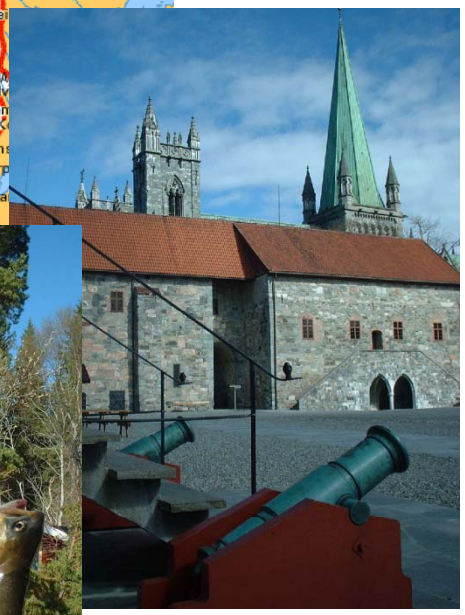


Genetic Epidemiology of Parkinson's Disease

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

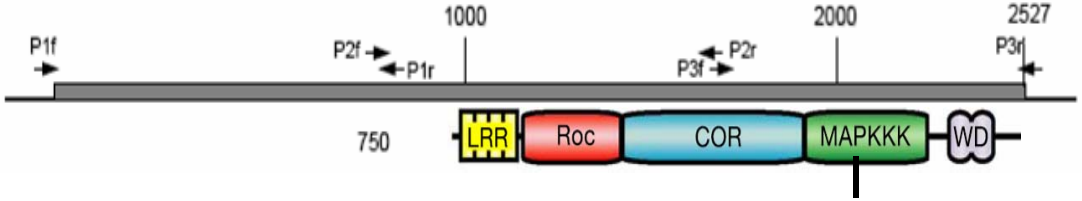
130 variants genotyped
MAF >0, n=66
2.8% missing genotypes in 14,702
Rare variants sequenced (MAF<1%)



Identification of a Novel *LRRK2* Mutation Linked to Autosomal Dominant Parkinsonism: Evidence of a Common Founder across European Populations

The American Journal of Human Genetics

2005



G2019S

```
LRRK2      DYGIAQ----YCCRMGIKTSEGTPGFRAPE
LRRK1      DYGISR----QSFHEGALGVEGTPGYQAPE
MATK       DFGLAK-----AERKGLDSSRLPVKWTAPE
PDGFRA     DFGLARDIMHDSNYVSKGSTFLPVKWMAPE
MAP3K10    DFGLAR----EWHKTTKMSAAGTYAWMAPE
DAPK1      DFGN----------EFKNIFGTPEFVAPE
BRAF       DFGLATVKSRWSGSHQFEQLSGSILWMAPE
```

	6055G>A G2019S Families													
Marker	**P-069**	**P-099**	**P-104**	**P-241**	**P-369**	**P-394**	**F05**	**1210**	**1120**	**111**	**3211**	**PD99**	**1P**	
D12S67	180	180	184	184		168	186	168/168	184	180	168	168/186	168/168	
D12S1648	120	120	122	122	122	110	110	122/124	110	110	110	120/134	128/130	
D12S2080	188	188	188	188	188	188	188	184/192	188	180	184	188/192	184/188	
D12S2194	285	285	285	285	285	285	281	253/281	257	257	253	245/249	249/281	
D12S2514	291	291	291	291	291	291	291	291	291	291	291	291/294	285/291	
D12S2515	224	224	224	224	224	224	224	220/224	224	224	224	218	212/220	
rs7966550	T	T	T	T	T	T	T	T	T	T	T	T	T	T
D12S2516	254	254	254	254	254	254	254	254	254	254	254	254	254	254
rs1427263	A	A	A	A	A	A	A	A	A	A	A	A	A	A
rs11176013	G	G	G	G	G	G	G	G	G	G	A/G	G	A/G	G
rs11564148	A	A	T/A	A	A	A	T/A	T/A	A	A	T/A	A	T/A	A
D12S2518	154	154	154	154	154	154	154	154	154	154	154	154	154	154
D12S2519	132	132	132	132	132	132	132	132	132	132	132/138	132/138	132/134	132
D12S2520	260	260	260	260	257/260	260	260	257/260	260	257/260	260	248/260	264/280	260
D12S2521	359	359	327/359	359	359	359	359	359/367	359	359	359	323/363	359/379	
D12S2522	297	297	297	297	297	297	297	297	297	297	295/297	281/297	297	
D12S2523	320	320	320	320	320	320	320	320	320	320	314/320	317/320	306/320	
D12S2517	190	190	190	190	190	190	190	190/194	194	194	192	194/190	184/188	
D12S1048	214	214	214	214	214	211/214	214	214/223	214	214	223	211/214	211/226	
D12S1301	112	118	120	120	118	118	118	108/118	100	120	118	100/118	100	
D12S1701	95	97	91	91	95	95/97	97	95/101	92	91/95	95	97/101	91/97	
	Norway							**United States**			**Ireland**		**Poland**	

<u>G2019S in “idiopathic” PD:</u>

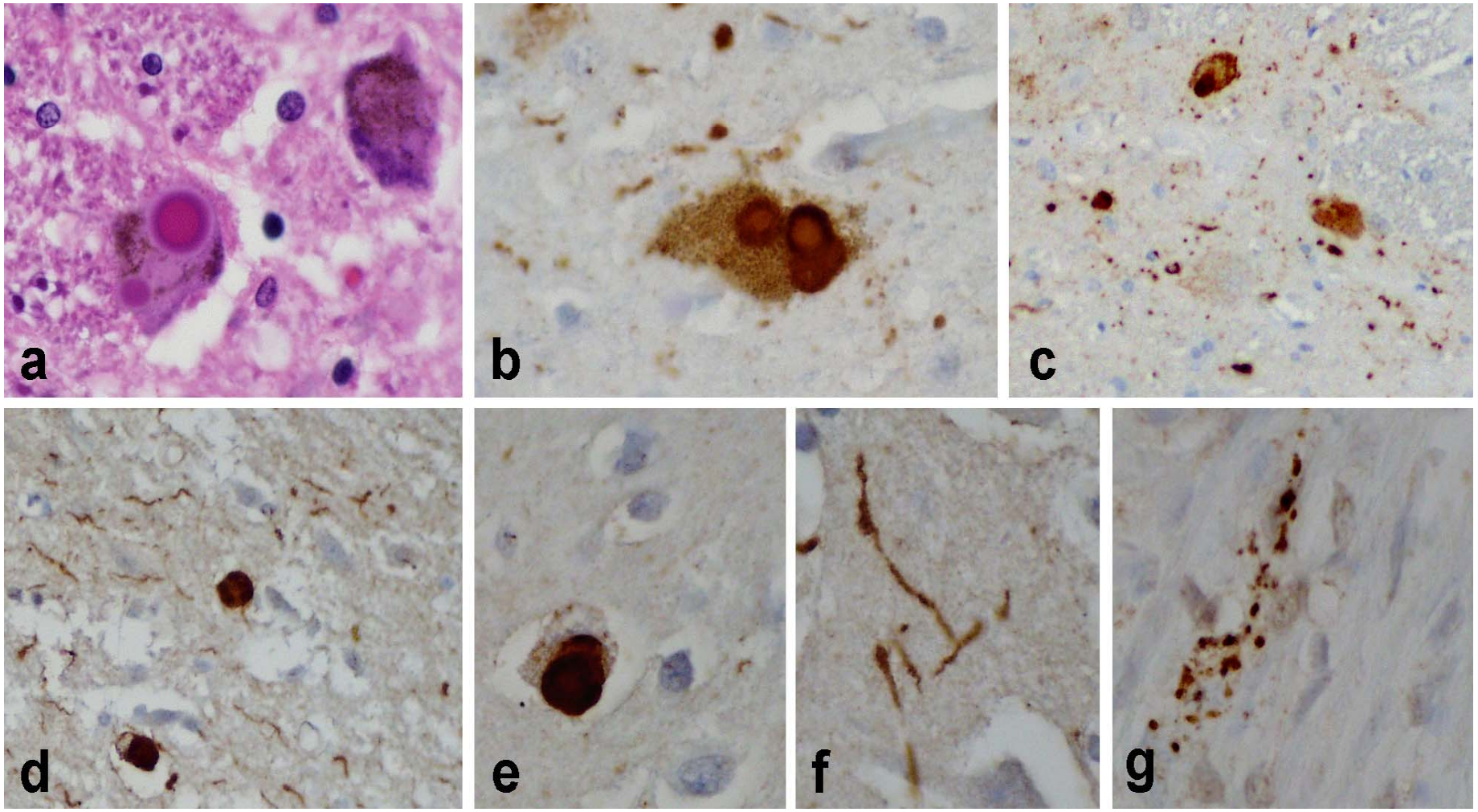
1% USA,

2.3% Norway,

5% Spain,

14% Ashkenazi Jews,

30% N. Africa (Berber-Arabs)



Lrrk2 and Lewy Body Disease

Annals of Neurology 2006

Owen A. Ross, PhD,[1] Mathias Toft, MD,[1]
Andrew J. Whittle, BSc,[1] Joseph L. Johnson, PhD,[1]
Spiridon Papapetropoulos, MD, PhD,[2]
Deborah C. Mash, PhD,[2] Irene Litvan, MD,[3]
Mark F. Gordon, MD,[4] Zbigniew K. Wszolek, MD,[5]
Matthew J. Farrer, PhD,[1] and
Dennis W. Dickson, MD [1,6]

NEUROLOGI

Donegal
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Bremen
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Österreich
Austria
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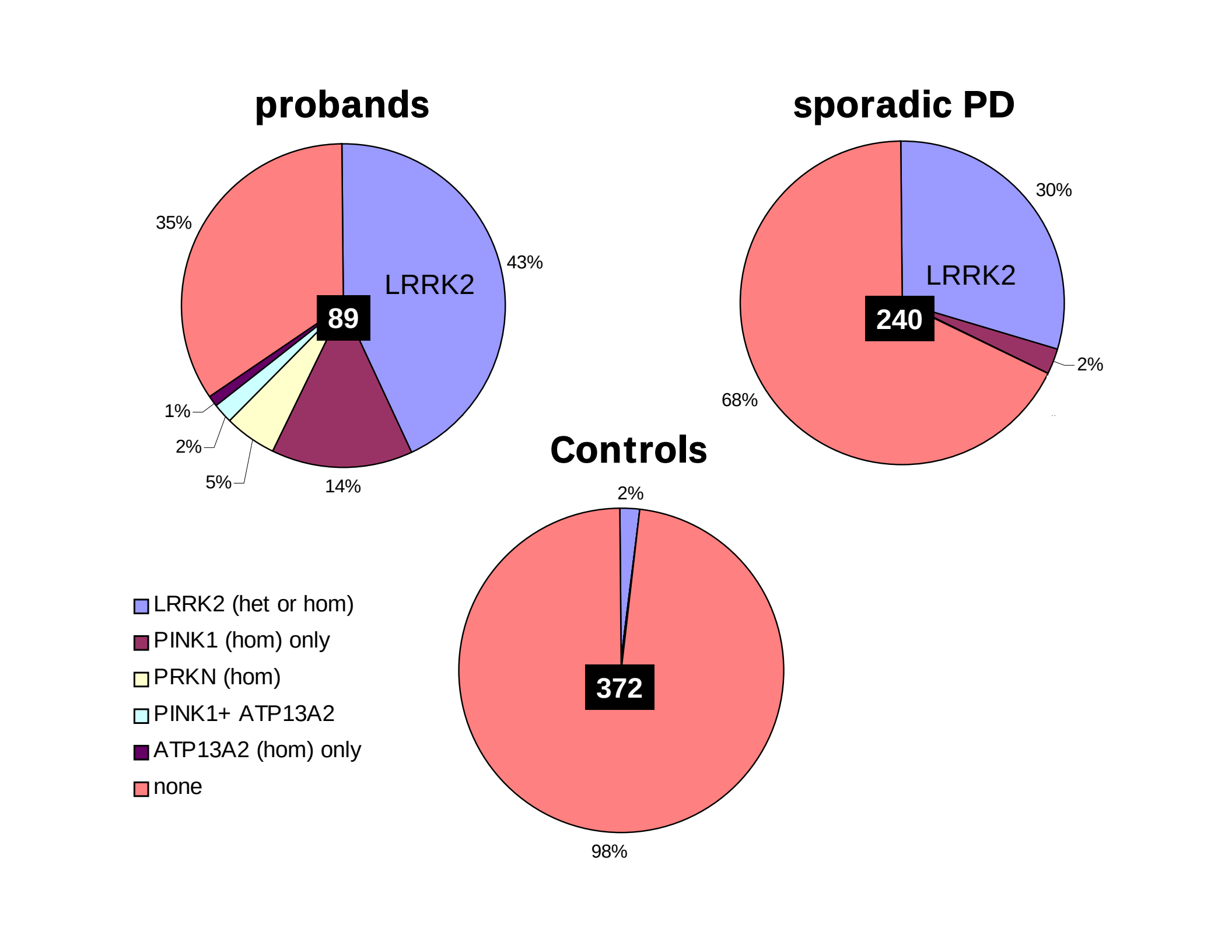
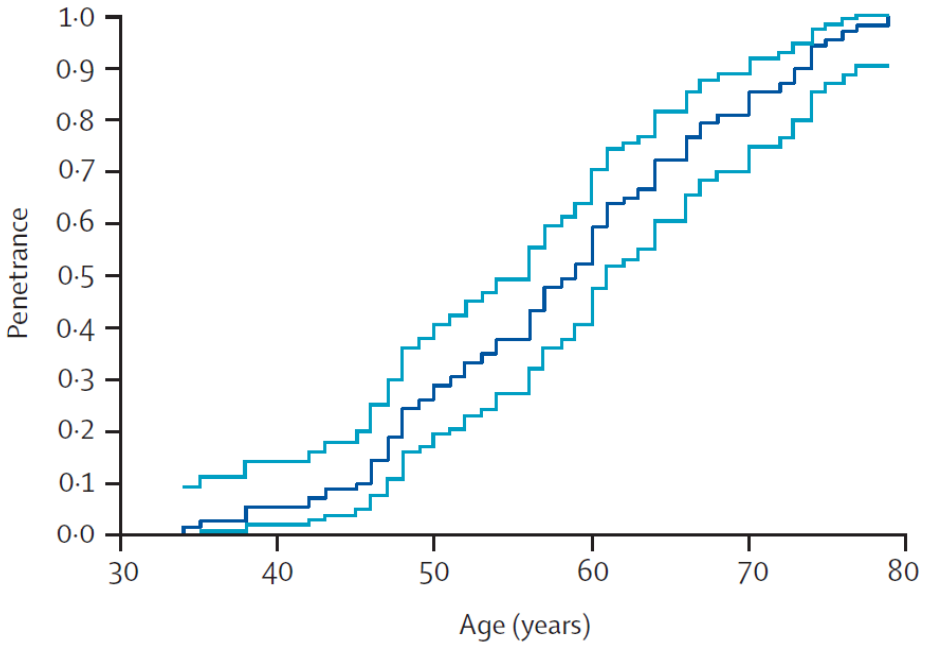
Athina
Αθήνα
El-Jazair
Tunis
Cádiz
Málaga
Oran
Antaly
Rabat
Tunisia
Dar-el-Beida
Tarabulus
Morocco
Algeria


probands
LRRK2
89
43%
35%
14%
5%
2%
1%
sporadic PD
LRRK2
240
30%
2%
68%
Controls
372
2%
98%
LRRK2 (het or hom)
PINK1 (hom) only
PRKN (hom)
PINK1+ ATP13A2
ATP13A2 (hom) only
none

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

THE LANCET Neurology



	LRRK2 Gly2019Ser homozygotes	LRRK2 Gly2019Ser heterozygotes	Without LRRK2 Gly2019Ser
N	12	60	166
Age at onset (SD), years	58·1 (9·5)	58·2 (11·0)	56·8 (13·2)
Median age of onset (IQR), years	57·5 (43·0–74·0)	60·0 (34·0–79·0)	60·0 (20·0–82·0)
Mean duration of PD, years	6·0 (2·9)	6·5 (5·4)	6·4 (5·4)
First symptom			
Tremor	11 (92%)	45 (75%)	115 (69%)
Deterioration in gait or balance	0 (0%)	6 (10%)	21 (13%)
Muscle cramping or dystonia	0 (0%)	1 (2%)	1 (<1%)
Other	1 (8%)	8 (13%)	29 (17%)
PD phenotype			
Akinetic-rigid	0 (0%)	10 (17%)	27 (16%)
Mixed	7 (58%)	41 (68%)	123 (74%)
Tremor-dominant	5 (42%)	9 (15%)	16 (10%)
Mean Hoehn and Yahr scale score			
On	2·8 (0·4) (n=2)	2·2 (0·8) (n=19)	2·4 (0·9) (n=48)
Off	2·3 (0·7) (n=8)	2·8 (0·9) (n=29)	2·7 (0·8) (n=83)
Mean Epworth scale score	0·6 (1·2) (n=12)	1·1 (2·4) (n=60)	1·2 (2·6) (n=166)
Mean UPDRS III scale score			
On	32·0 (1·4) (n=2)	45·7 (16) (n=19)	48·8 (19·3) (n=48)
Off	48·0 (12·6) (n=8)	66·0 (25·0) (n=29)	60·6 (19·6) (n=83)
Levodopa agonist treatment	11 (92%)	51 (85%)	136 (83%)

Data are number (%), mean (SD) (number of patients), or median (IQR).

Parkinson's Disease In Tunisia

Enrollment

1.Individual Information
2. Informed Consent
3.End Of Study Record
4.Inclusion\Exclusion Criteria
5. Family Information
6. Family Origin
7. Family Medical History
8. Vital Signs
9. PD Diagnostic Criteria

UPDRS

10. Complex Behaviors
11. nM-EDL
12. M-EDL
13. Motor Examination
14. Motor Complications
15. Score sheet

Medications

16. PD Medication Profile
17. Non-PD Medication
18. RG Levodopa

Non-motor

19. SCOPA-AUT
20. Epworth Sleepiness Scale
21. Olfactory Testing
    - 21.1. PD Criteria
    - 21.2. Control Criteria
    - 21.3. Clinical History
    - 21.4. Assessment
    - 21.5. Identification
    - 21.6. Threshold
22. Schwab & England

Cognitive Testing

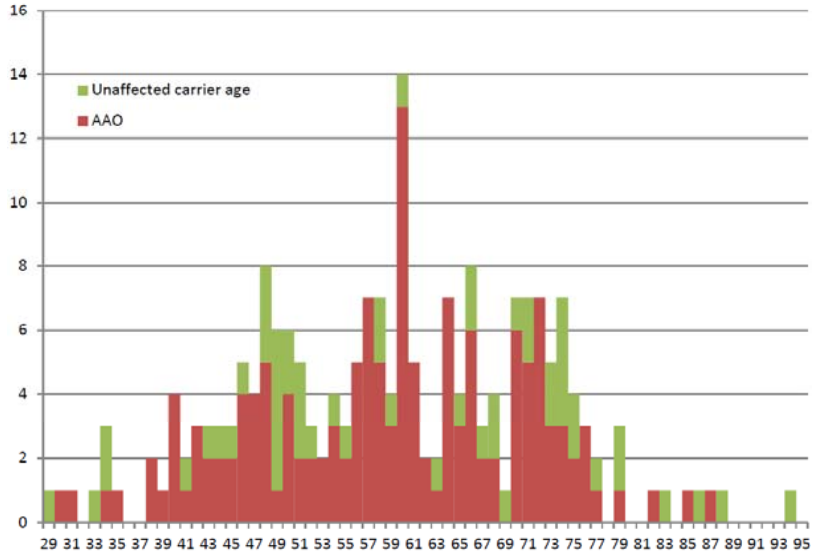
23. Mini-Mental State Examination (MME)
24. MOCA
25. Six Picture Test
26. FAB
27. Genetic Depression Scale (GDS)

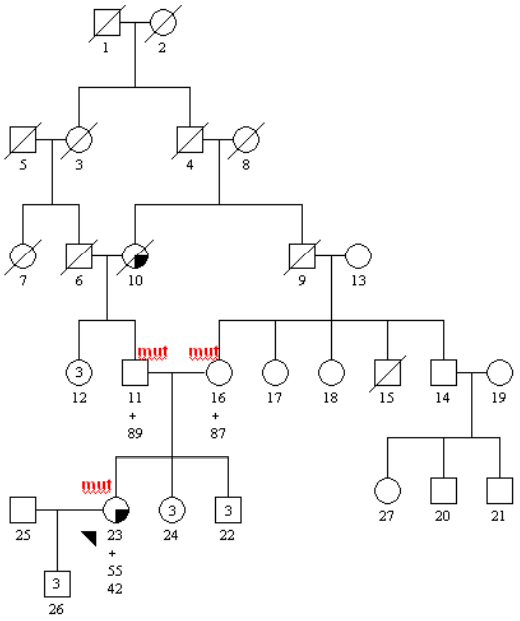
Environment and Lifestyle

28. Geoparkinson Questionnaire
29. Pesticides at Work
30. Pesticides in Non-Working Settings
31. Smoking and Tobacco
32. Caffeine

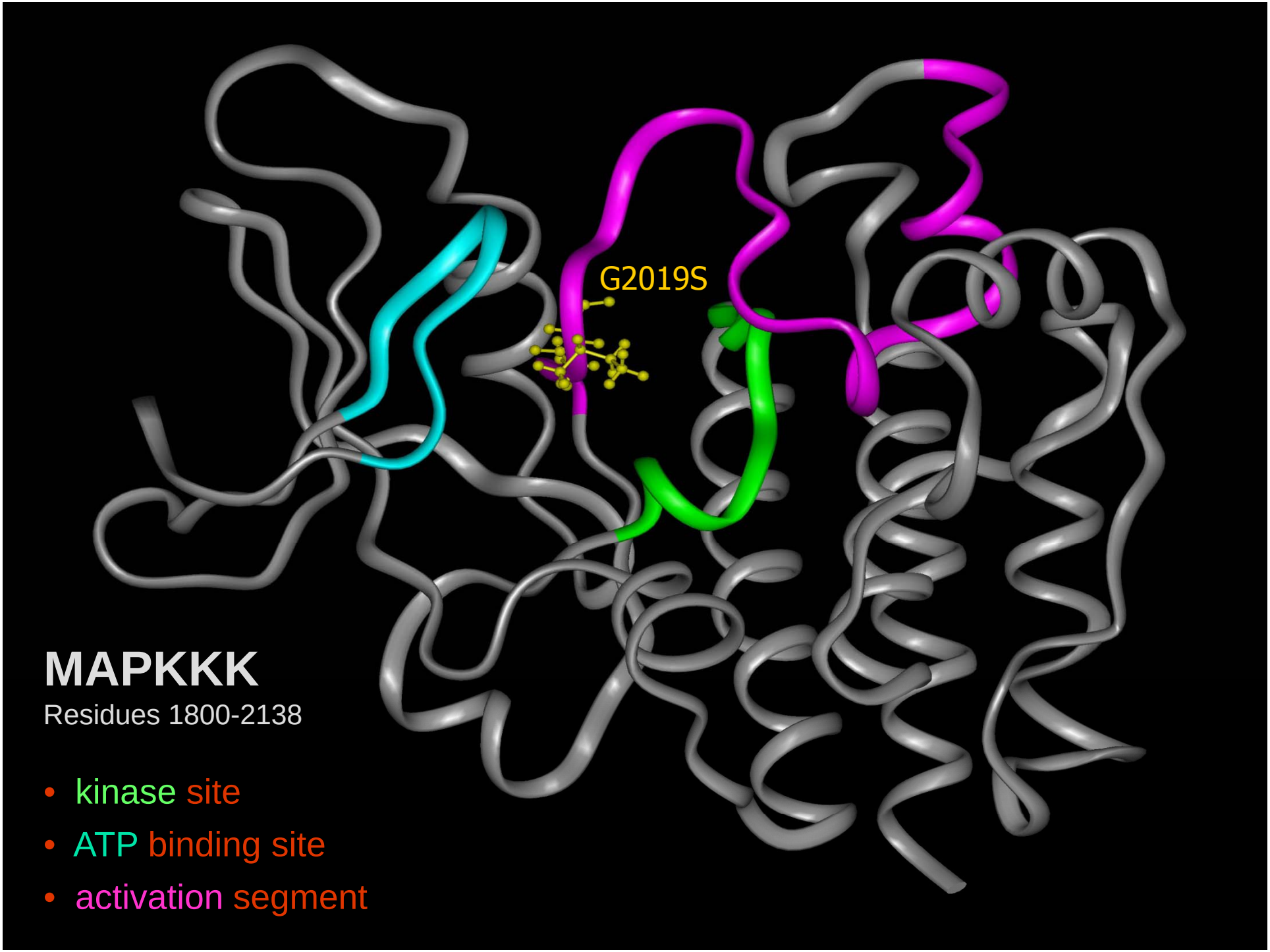
Tunisian PD Lrrk2 G2019S - Penetrance modifiers?

258 multi-incident kindreds
(40 with longitudinal evaluation)



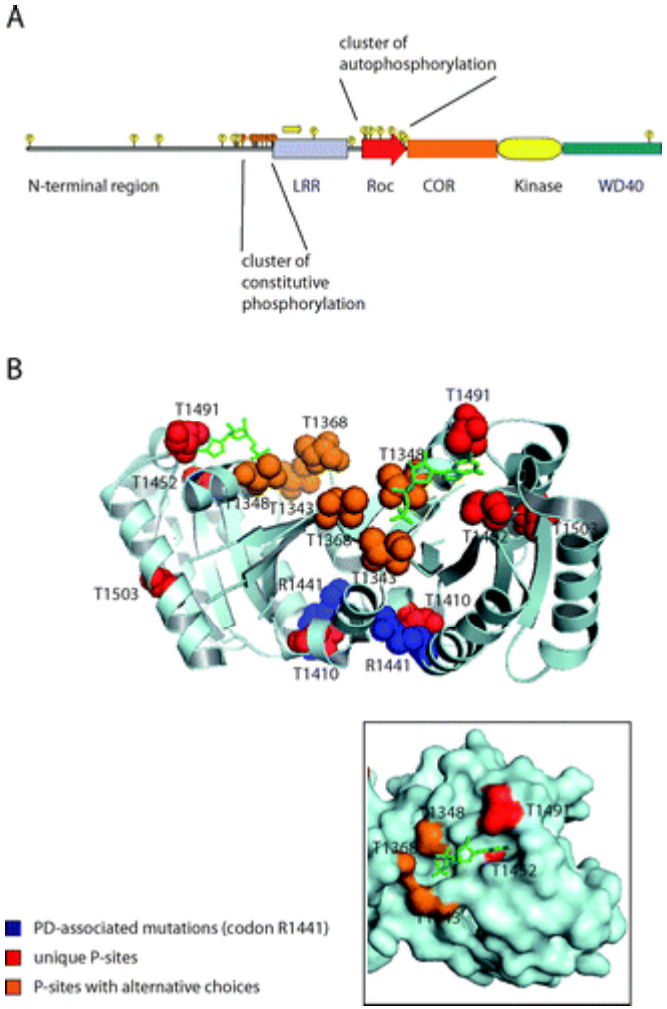


No G2019S


G2019S
MAPKKK
Residues 1800-2138
kinase site
ATP binding site
activation segment

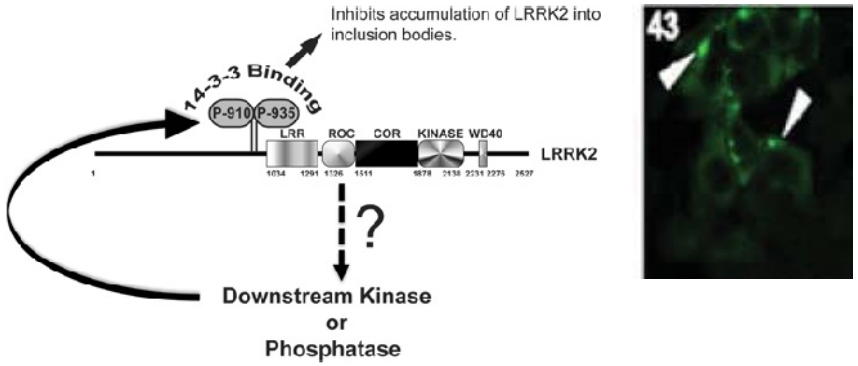
research articles Journal of proteome research 2010

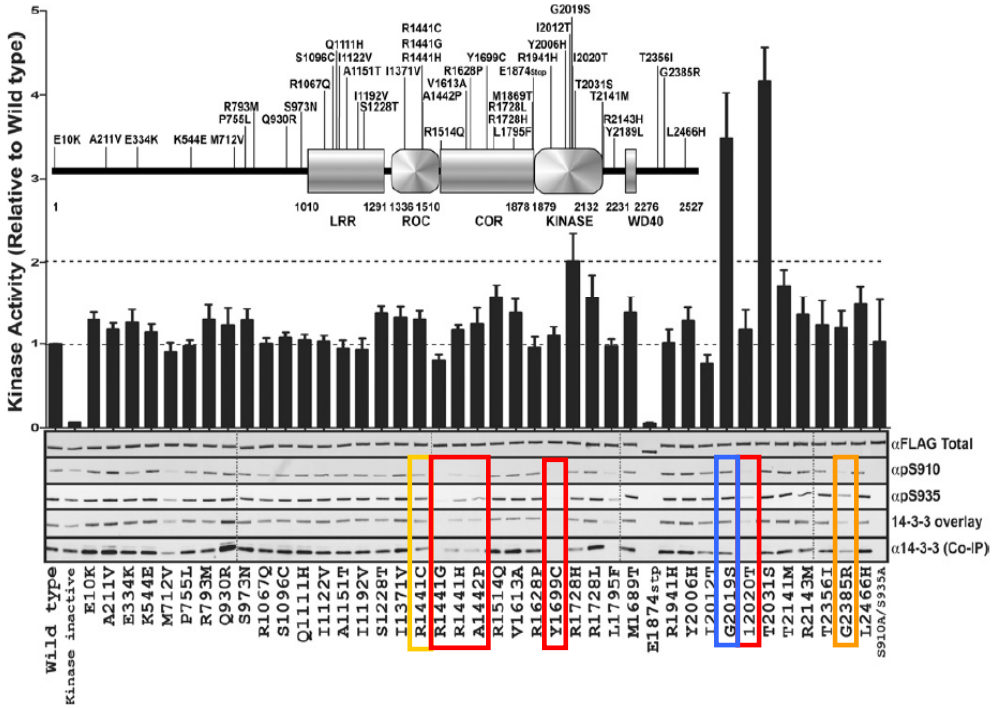
Phosphopeptide Analysis Reveals Two Discrete Clusters of Phosphorylation in the N-Terminus and the Roc Domain of the Parkinson-Disease Associated Protein Kinase LRRK2



BJ 2010

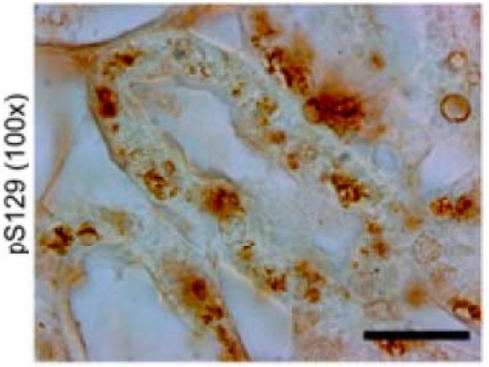
Inhibition of LRRK2 kinase activity leads to dephosphorylation of Ser^{910}/Ser^{935}, disruption of 14-3-3 binding and altered cytoplasmic localization





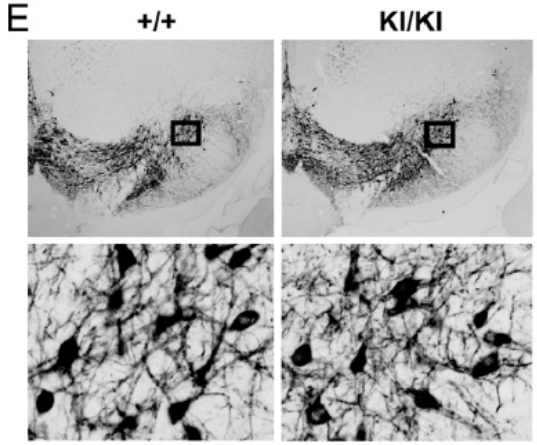
Loss of leucine-rich repeat kinase 2 causes impairment of protein degradation pathways, accumulation of α-synuclein, and apoptotic cell death in aged mice

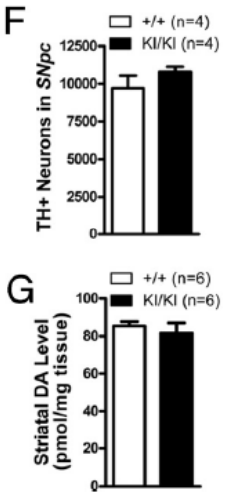
PNAS 2010

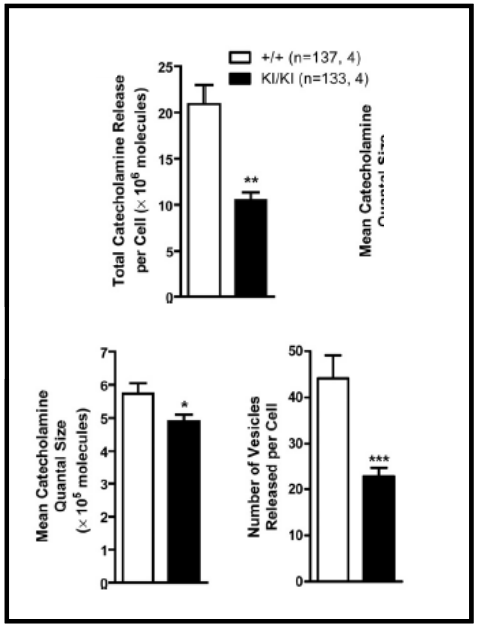


R1441C mutation in LRRK2 impairs dopaminergic neurotransmission in mice

PNAS 2009

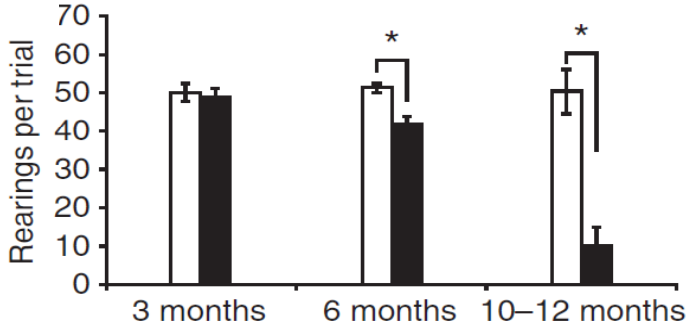




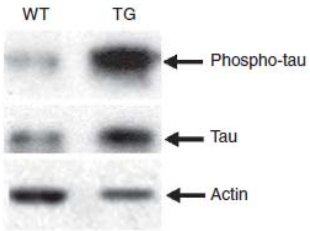


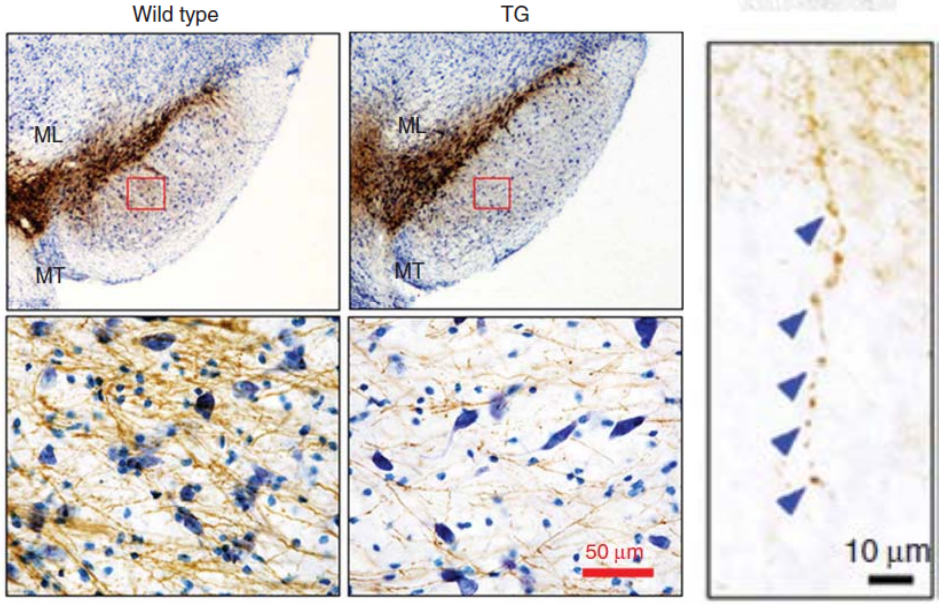
NATURE NEUROSCIENCE 2009

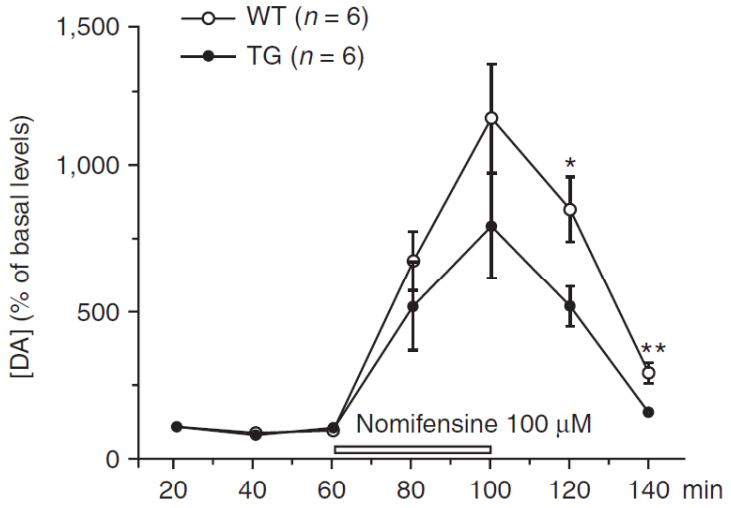
Mutant *LRRK2*^{R1441G} BAC transgenic mice recapitulate cardinal features of Parkinson's disease



LRRK2^{R1441G} BAC mice develop age-dependent motor deficits

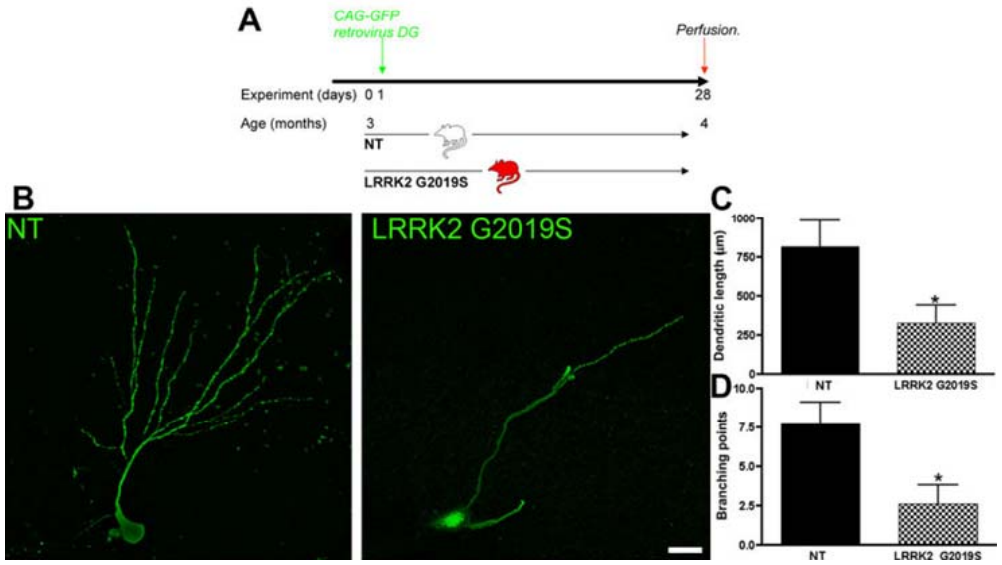


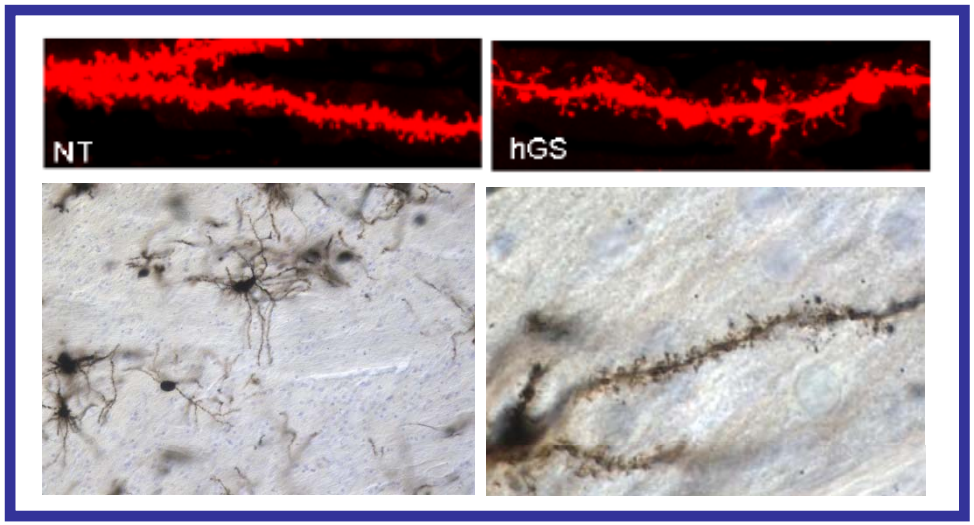


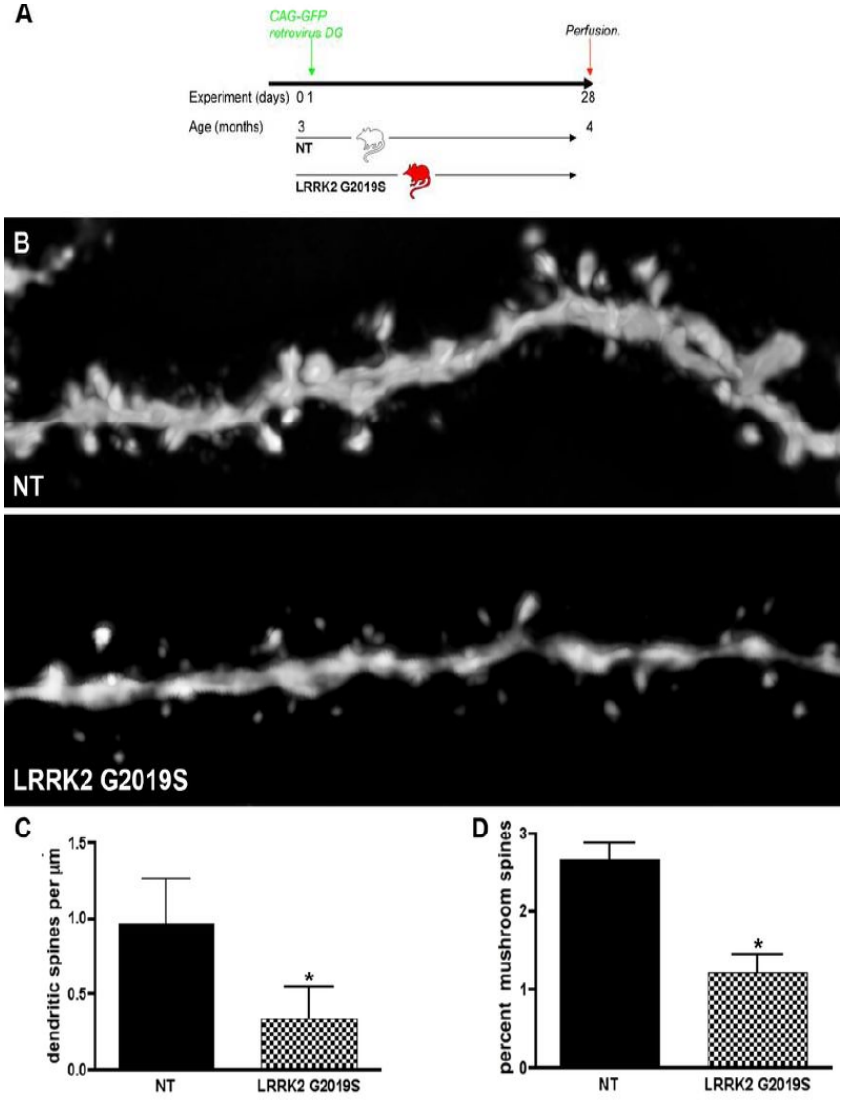


Neurochemical deficits in *LRRK2*^{R1441G} mice.

LRRK2 in spine spine density and morphology

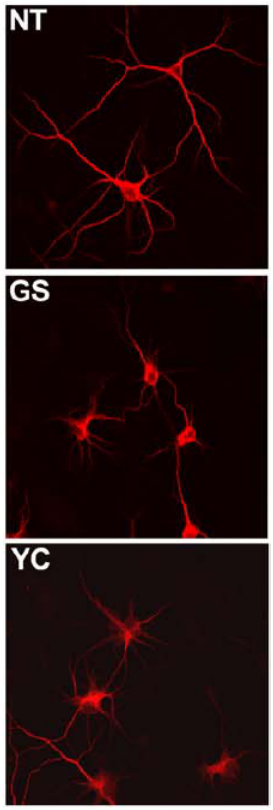


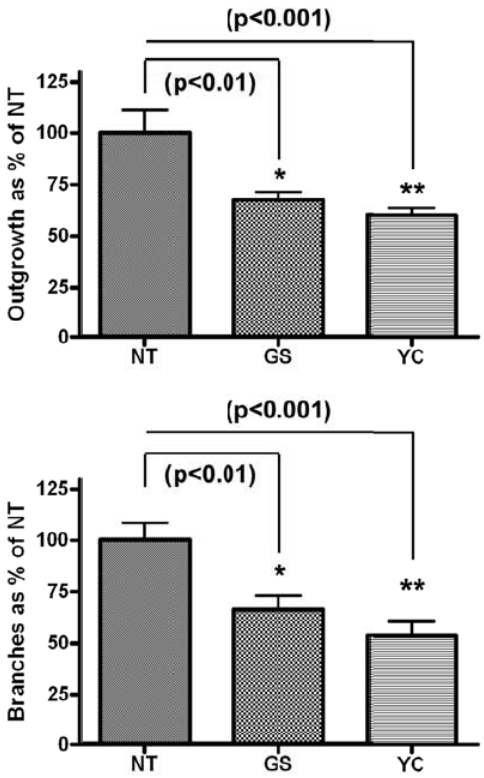


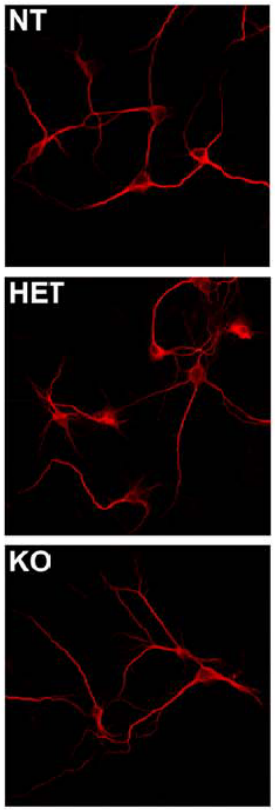


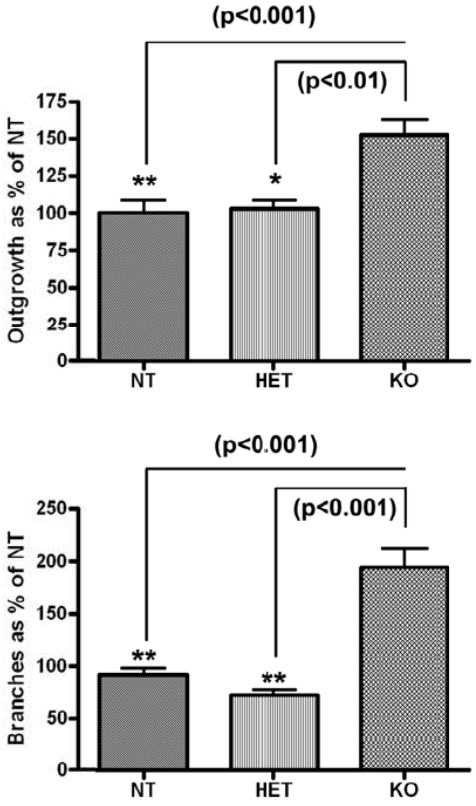
Heather Melrose/Beate Winner/Fred Gage

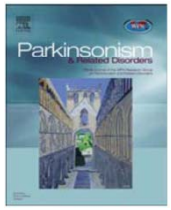
A comparative study of Lrrk2 function in primary neuronal cultures☆







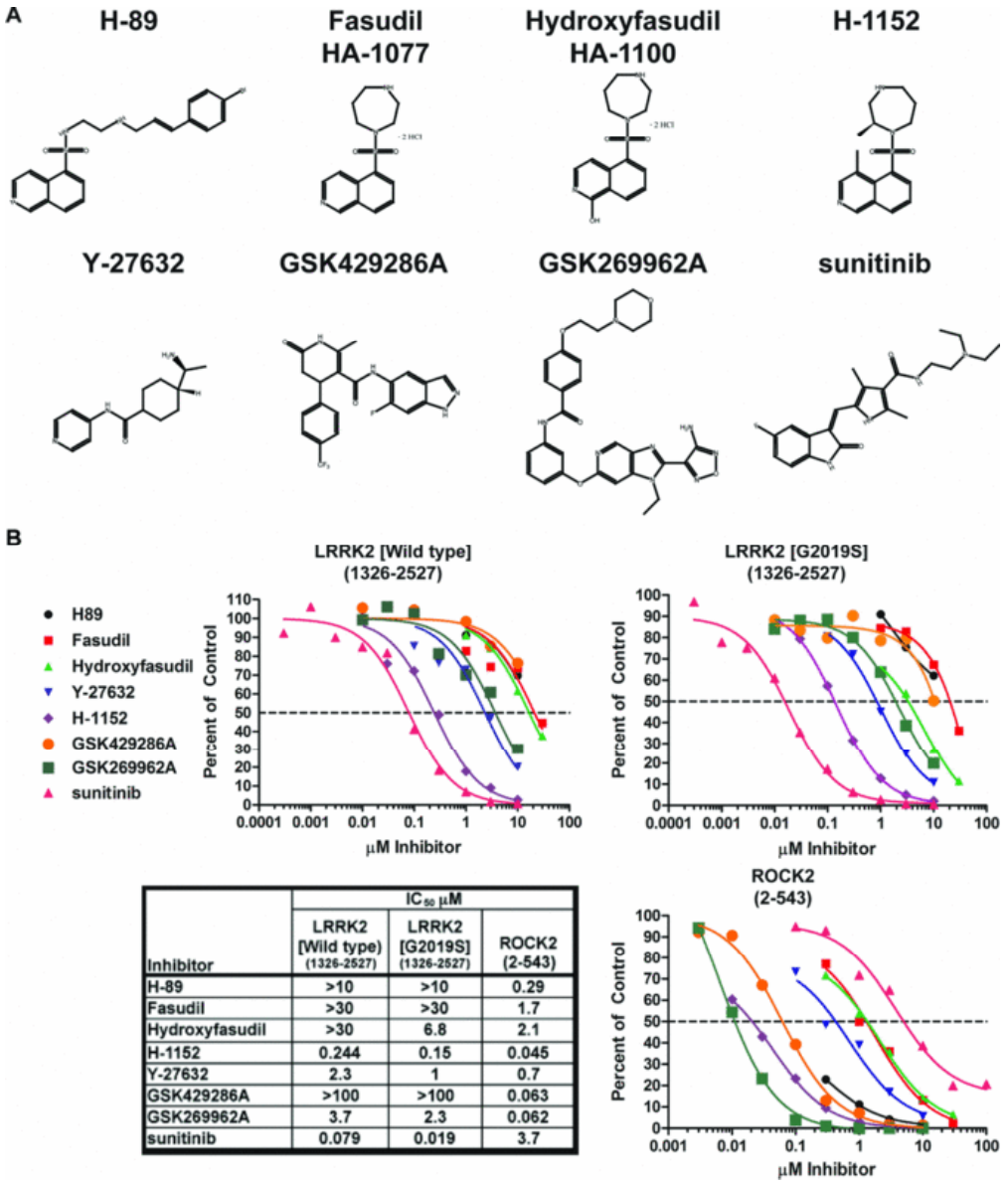




2010

The Familial Parkinsonism Gene *LRRK2* Regulates Neurite Process Morphology

Neuron 2006



Inhibitor	IC_{50} µM		
	LRRK2 [Wild type] (1326-2527)	LRRK2 [G2019S] (1326-2527)	ROCK2 (2-543)
H-89	>10	>10	0.29
Fasudil	>30	>30	1.7
Hydroxyfasudil	>30	6.8	2.1
H-1152	0.244	0.15	0.045
Y-27632	2.3	1	0.7
GSK429286A	>100	>100	0.063
GSK269962A	3.7	2.3	0.062
sunitinib	0.079	0.019	3.7

Biochemical Journal (2009) 424, 47-60 - R. Jeremy Nichols, Nicolas Dzamko and others.

www.biochemj.org

Parkinson's disease

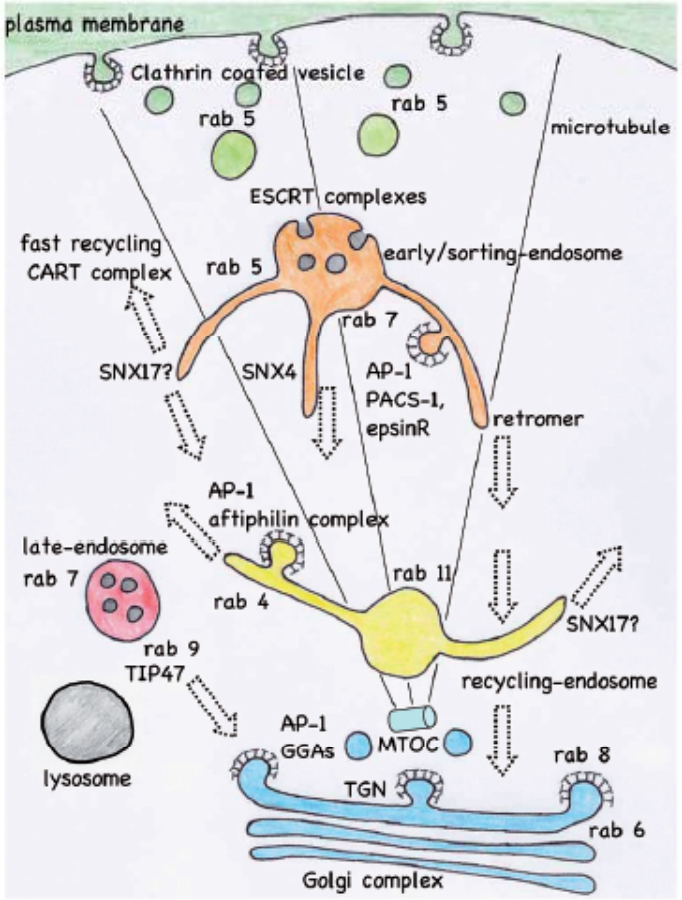
EIF4G1: (D) 3q27
SNCA: (D/S) 4q21
LRRK2: (D) 12p12

Parkinsonism

DJ-1: (R) 1p36
PINK1: (R) 1p35-p36
PRKN: (R/S) 6q25.2-q27
VPS35: (D) 16q25

Atypical parkinsonism

ATP13A2: **(R) 1p36**
GBA: **(S) 1q22**
DCTN1: **(D) 2p14**
MAPT**: (D/S?) 17q21**
PRGN **(D) 17q21**
SCA2, SCA3, SCA6 **etc.**
….and PARK loci



2006

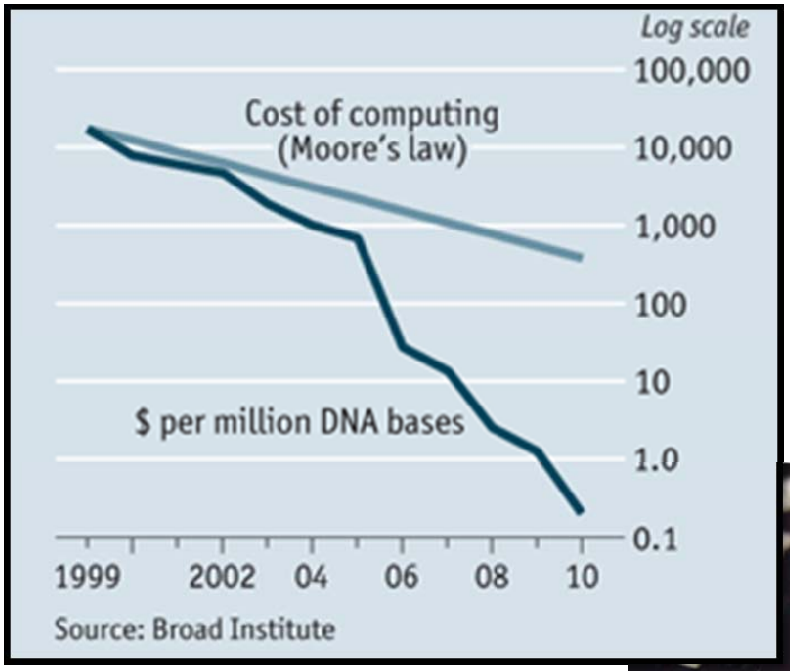
NATURE REVIEWS | GENETICS

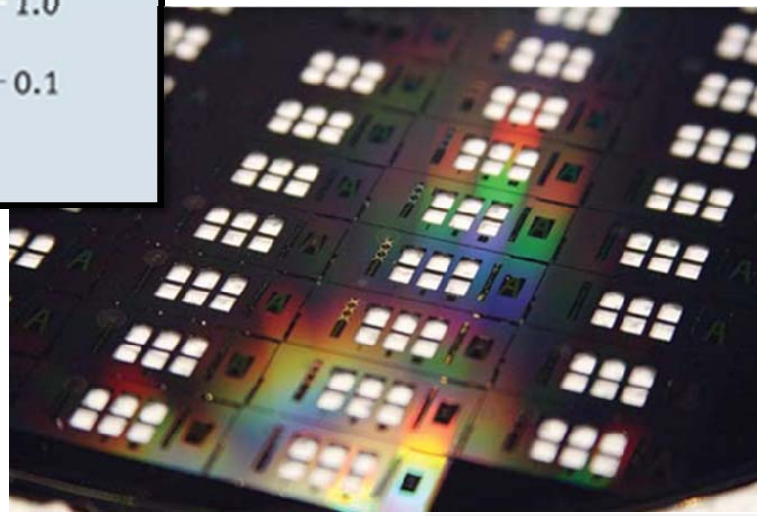
Genetics of Parkinson disease: paradigm shifts and future prospects

Matthew James Farrer

- Countries
  - Australia
  - Belgium
  - Canada
  - Chile
  - Egypt
  - England
  - France
  - Germany
  - Greece
  - Ireland
  - Israel
  - Italy
  - Japan
  - Jordan
  - Korea
  - Norway
  - Poland
  - Singapore
  - South Africa
  - Spain
  - Sweden
  - Switzerland
  - Taiwan
  - Tunisia
  - USA
  - Yemen

Next generation sequencing for neurological disorders





Centre for Molecular Medicine and Therapeutics

CHILD & FAMILY RESEARCH INSTITUTE

Pacific Parkinson's Research Centre

Brain Research Centre

UBC FACULTY OF MEDICINE