MALADIE DE PARKINSON : APPORTS DE LA GENETIQUE

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Parkinson's disease

- Prevalence: 200 per 100,000

Age	*< 40*	*> 60*	*>85*
%	*Rare*	*1*	*4*

- Incidence: 20 per 100,000 annually
- Male > female

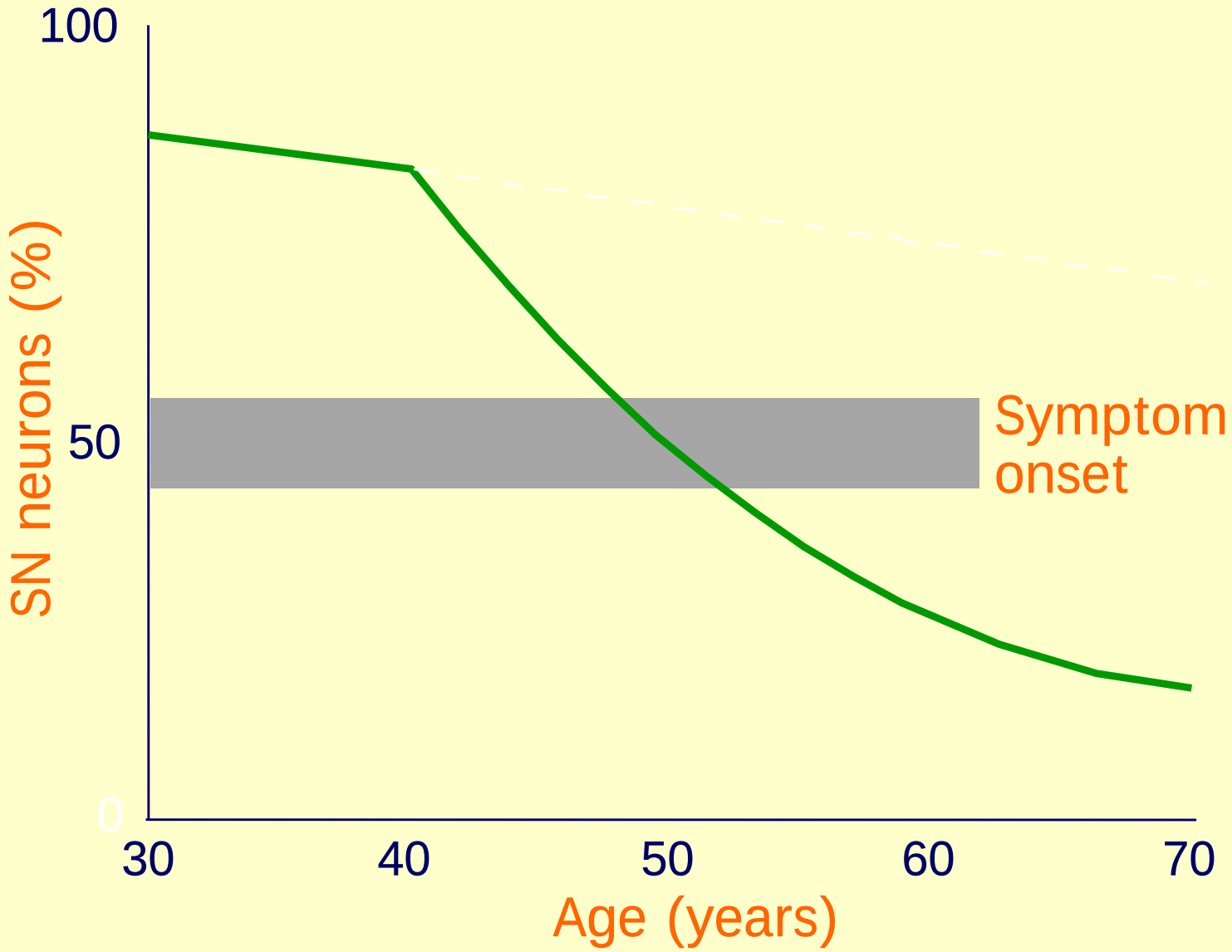
Parkinson's disease

Neurodegenerative disease characterized by:

- Bradykinesia
- Rigidity
- Rest tremor
- Good initial reactivity to levodopa

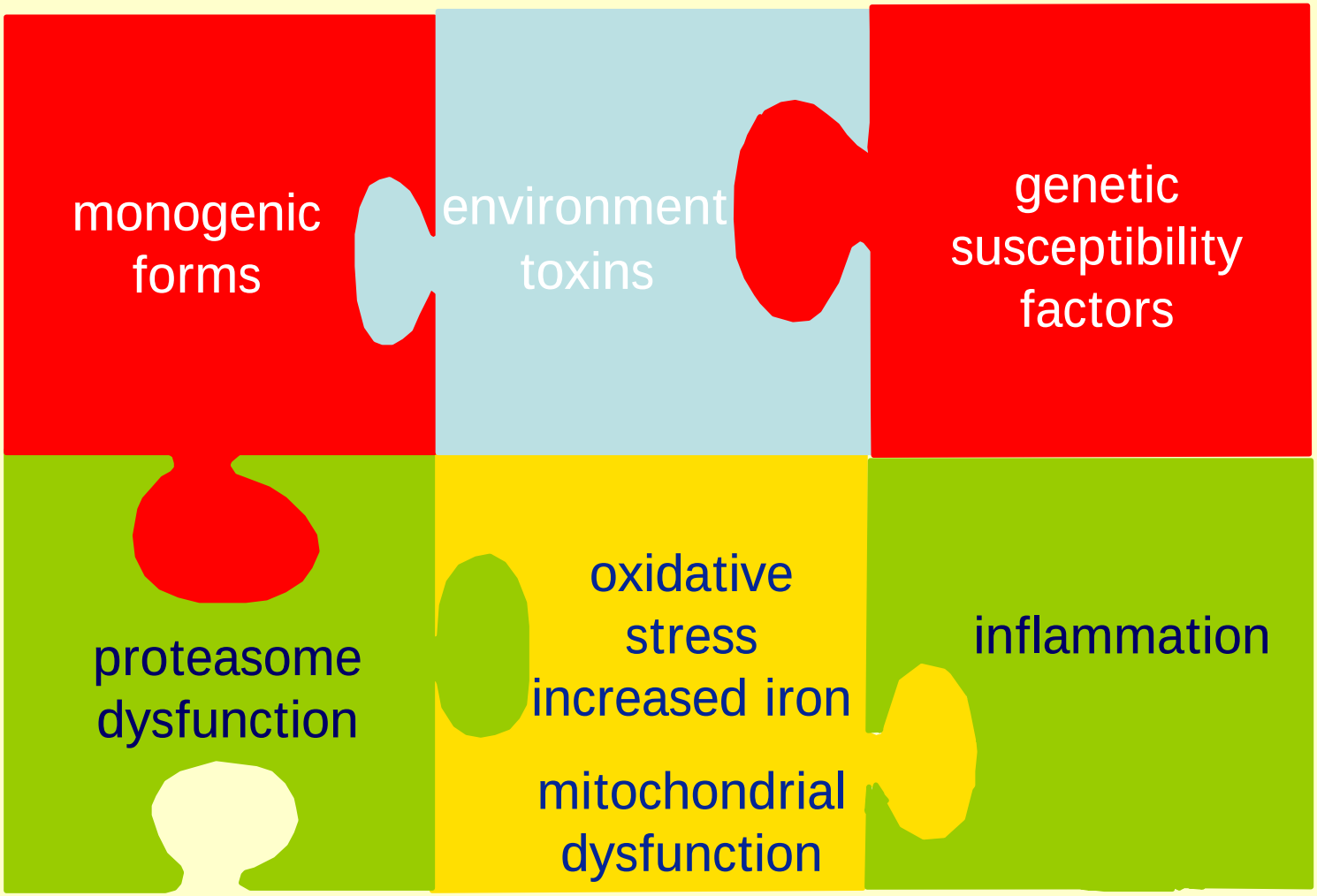
- Selective degeneration of the nigrostriatal dopaminergic pathway
- Lewy bodies

PROGRESSION OF PARKINSON'S DISEASE

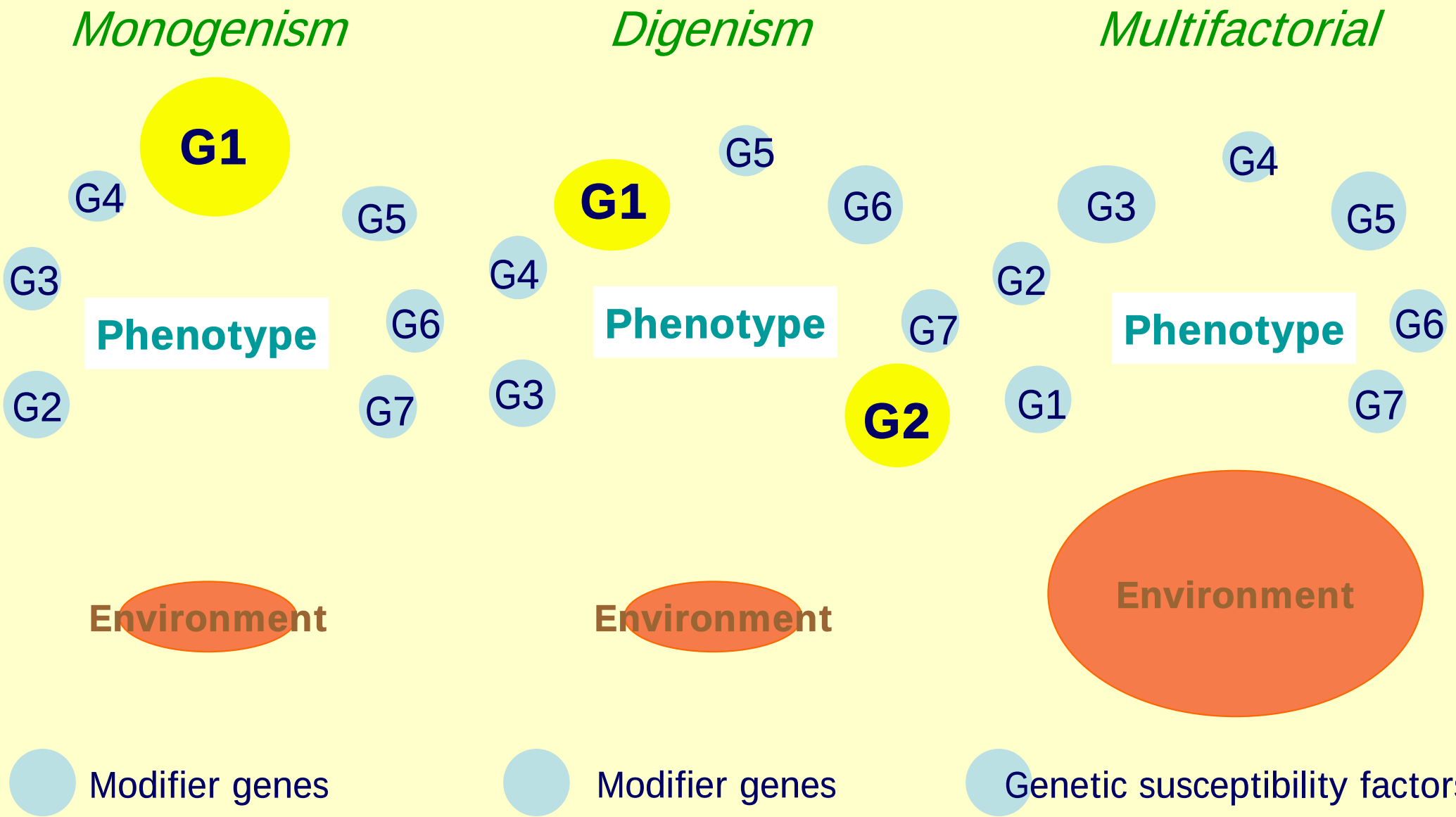


From Schulzer *et al*. Brain 1994;117:509-516

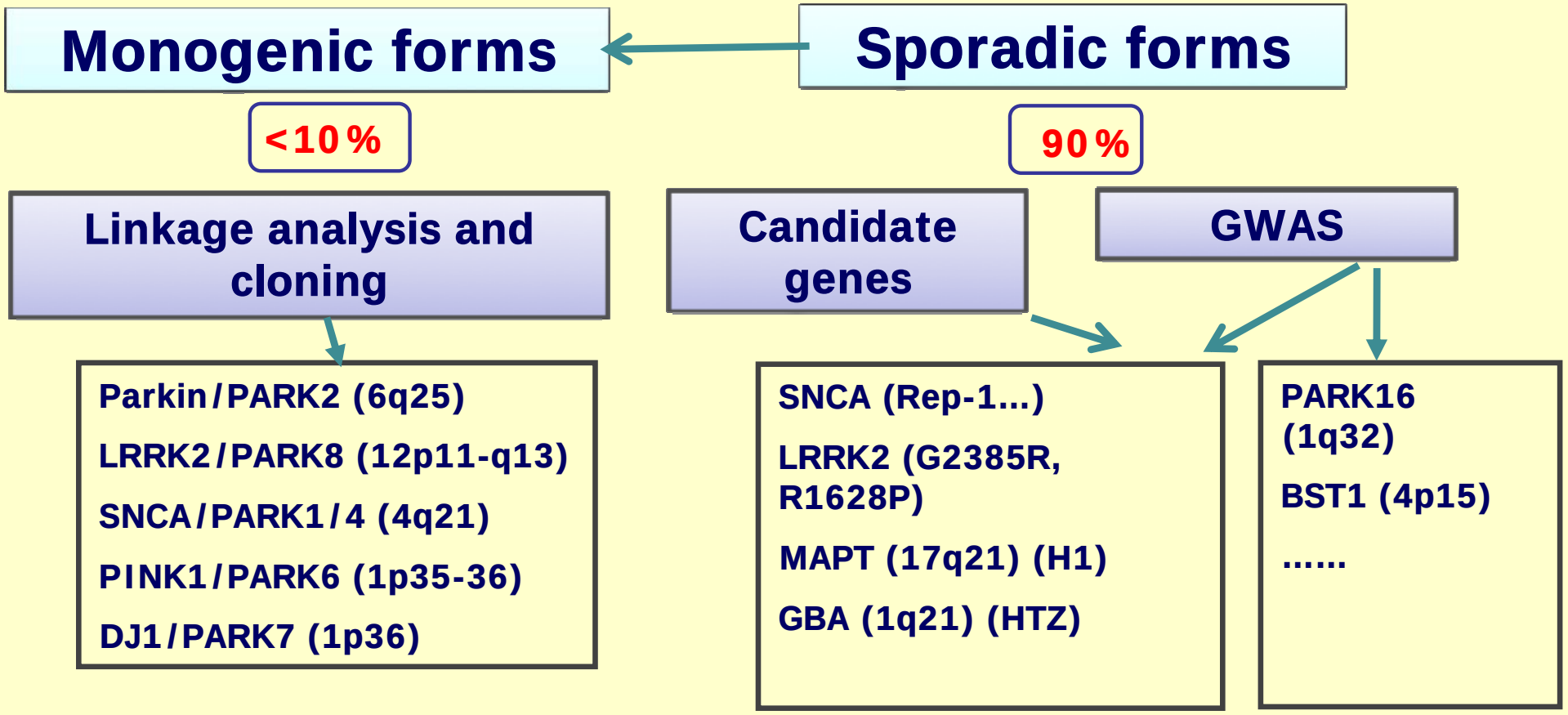
ETIOLOGY OF PARKINSON'S DISEASE



FROM MONOGENIC TO MULTIFACTORIAL DISORDERS : A CONTINUUM?



PARKINSON'S DISEASE AND GENETIC FACTORS

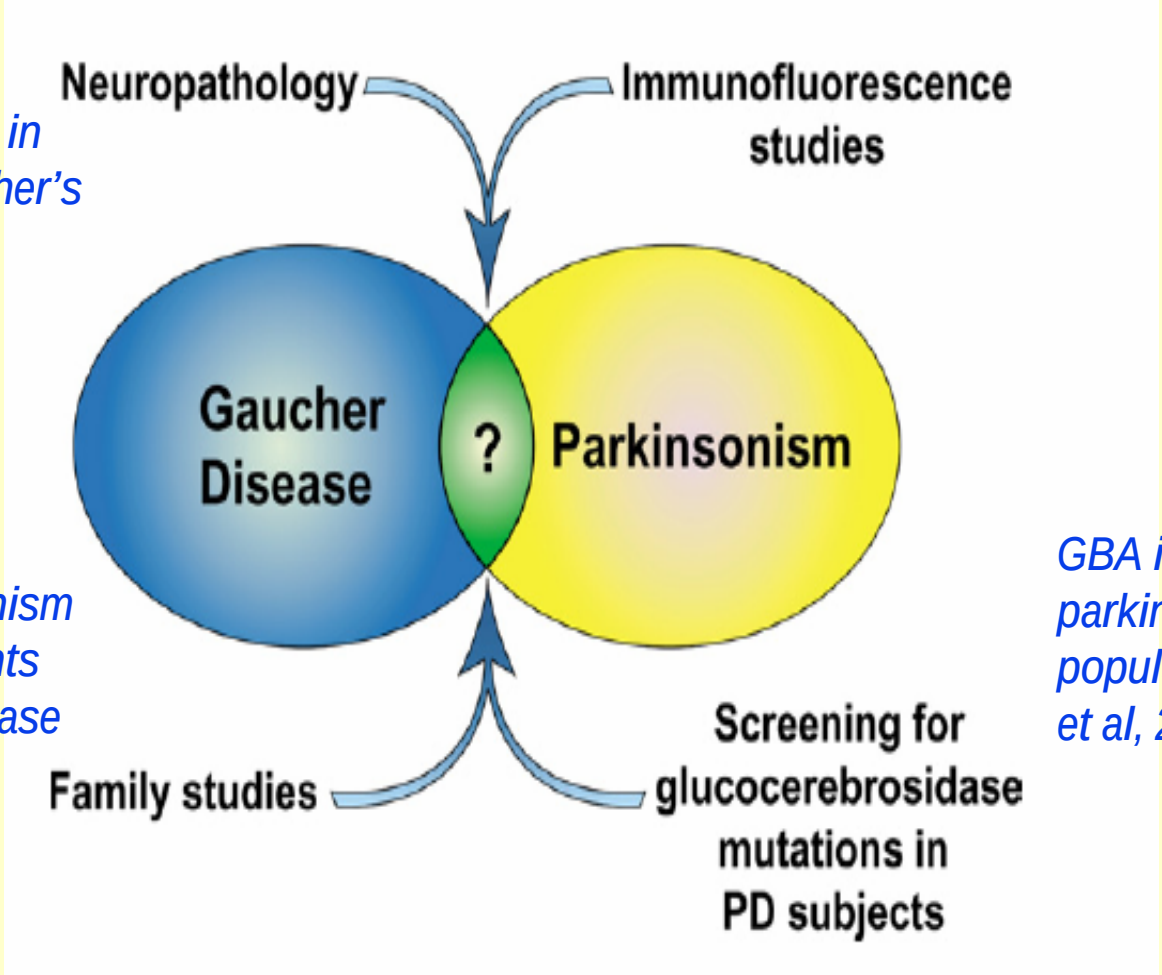


GAUCHER DISEASE
AUTOSOMAL RECESSIVE LYSOSOMAL DISEASE

Gaucher type	1	2	3
Age at onset	Childhood/Adult	Infancy	Childhood
Hepato-splenomegaly	+ to +++	++ to +++	+ to +++
Skeletal abnormalities	+ to +++	- to++	++ to +++
Neurological signs	- (except PD)	+++ Bulbar signs, ophtalmoplegia	+ to +++ Ocular apraxia, PME
Populations	Ashkenazi Jews	All	Sweden

GAUCHER DISEASE AND PARKINSON'S DISEASE ASSOCIATION

Lewy bodies found in patients with Gaucher's disease and parkinsonism



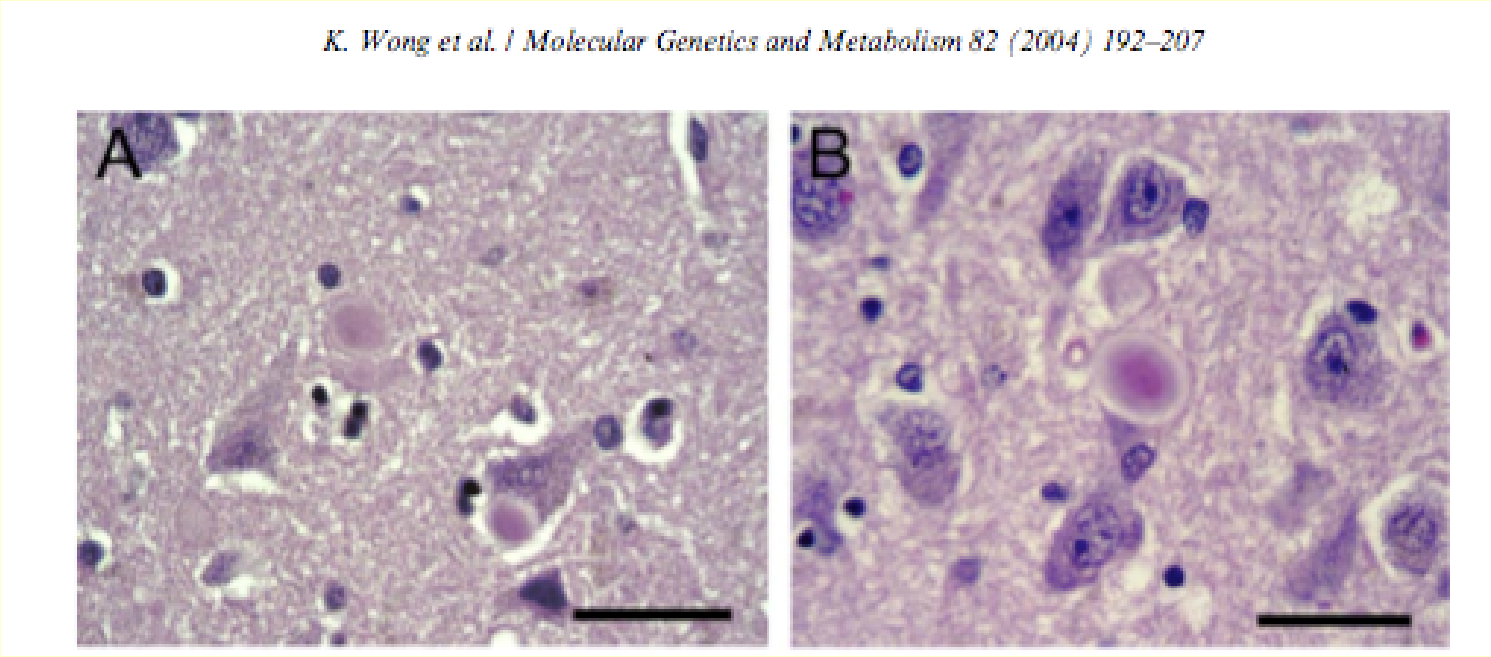
Increased parkinsonism in relatives of patients with Gaucher's disease

GBA is a risk factor for parkinsonism in various populations (Sidransky et al, 2009)

Sidransky *et al., 2009*

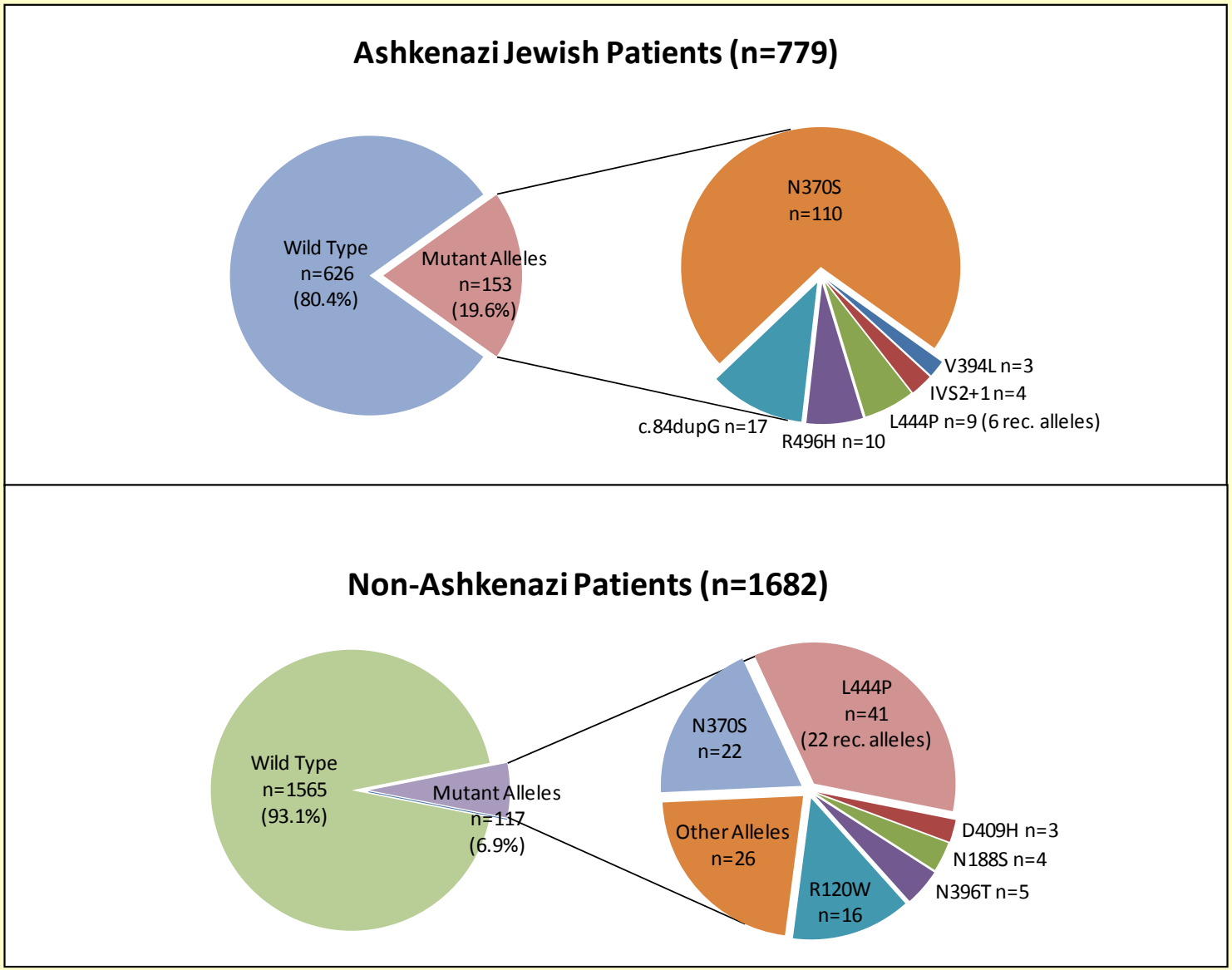
GBA AND NEURODEGENERATIVE DISORDERS

➢ Parkinsonism or dementia with lewy bodies associated with Gaucher disease



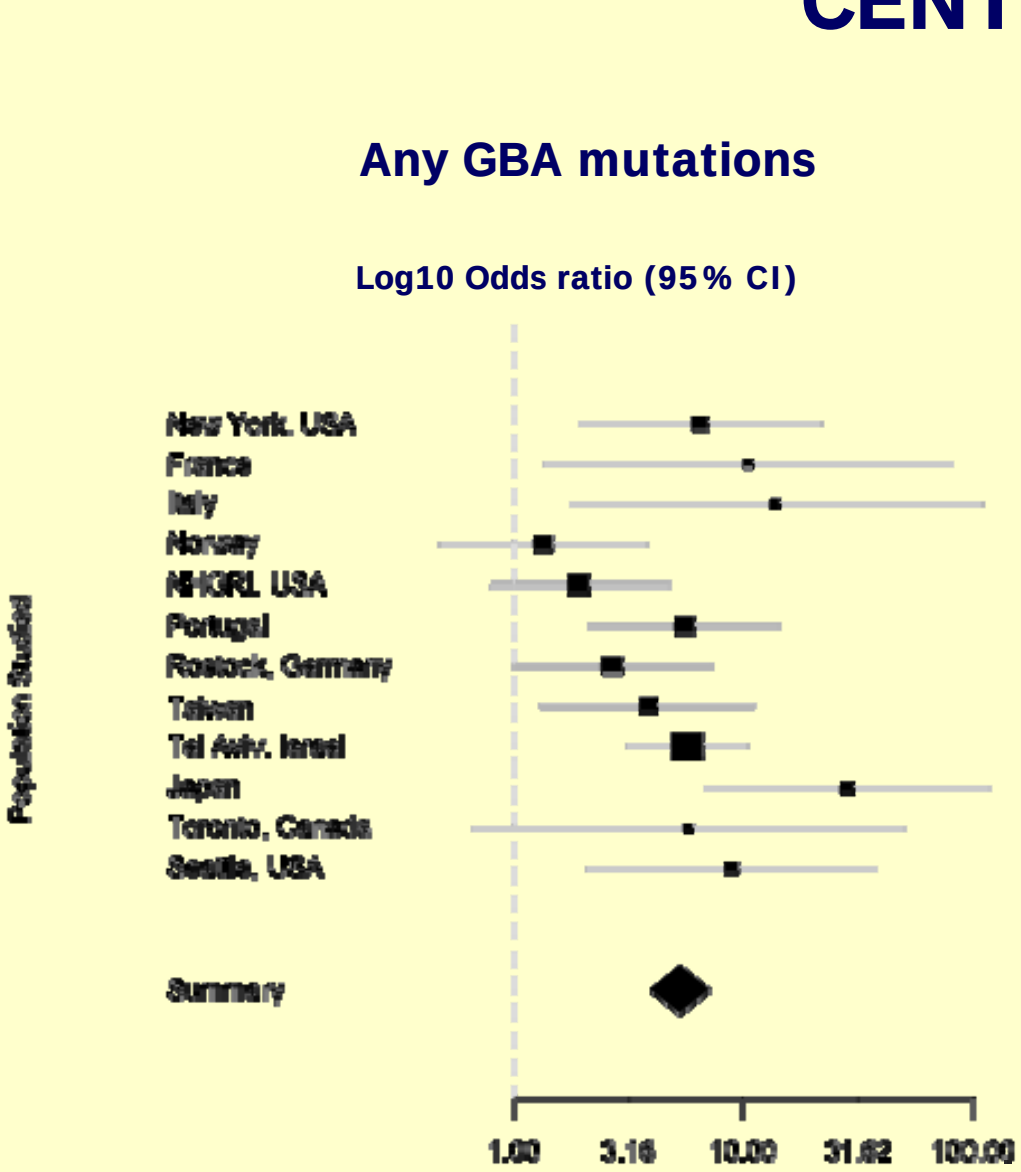
CA2 **CA3**

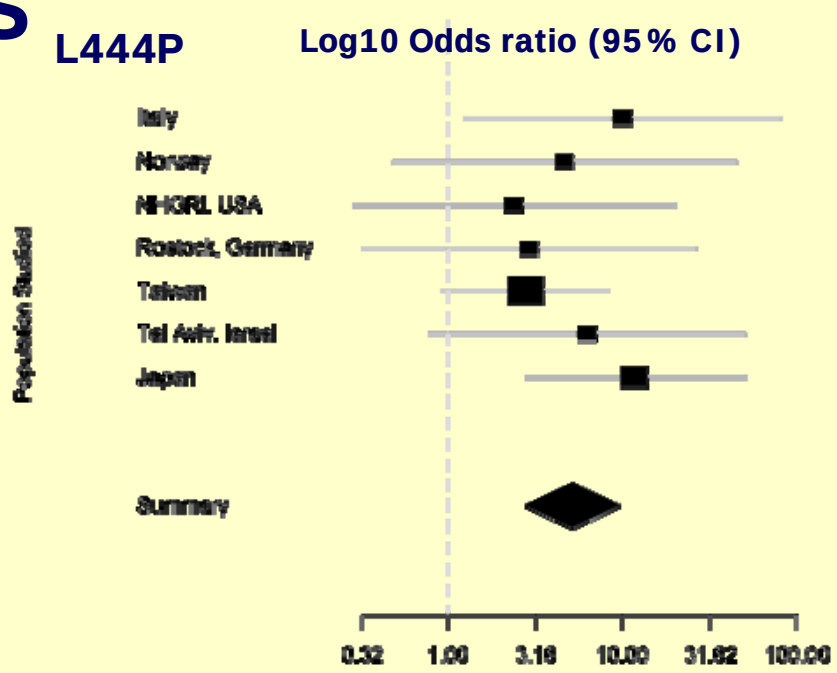
DISTRIBUTIONS OF GBA MUTATIONS AMONG THE MULTICENTER STUDY PATIENTS

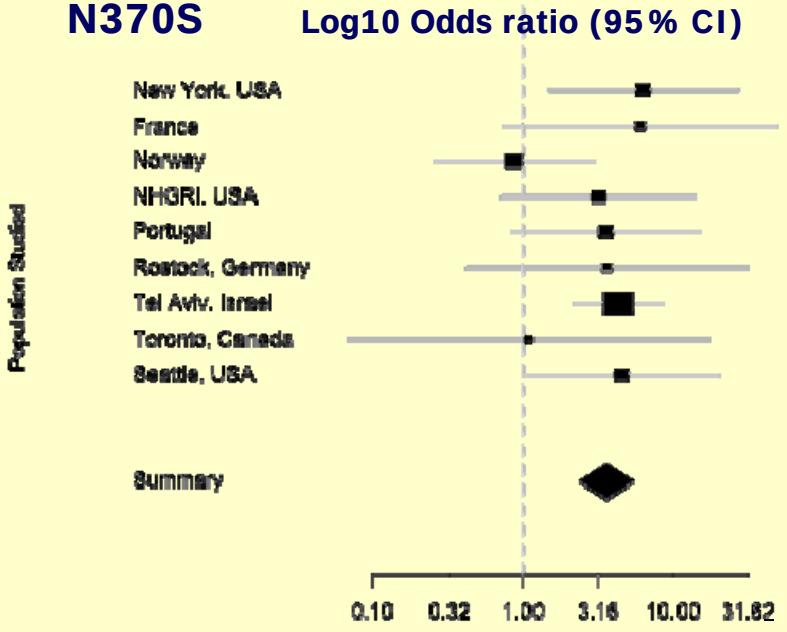


Sidransky *et al,* NEJM, 2009

ESTIMATE OF GBA RISK IN PARTICIPATING CENTERS

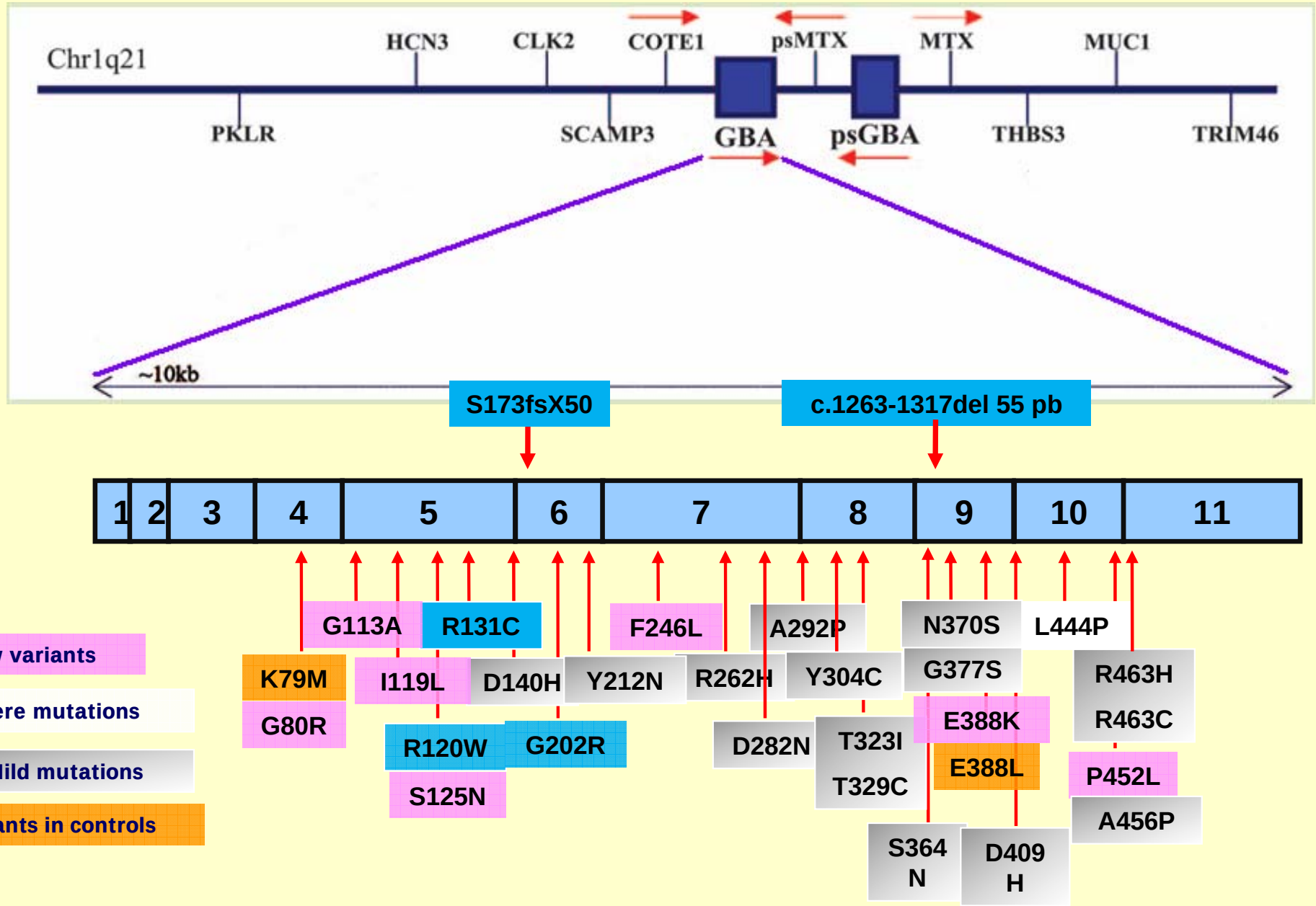






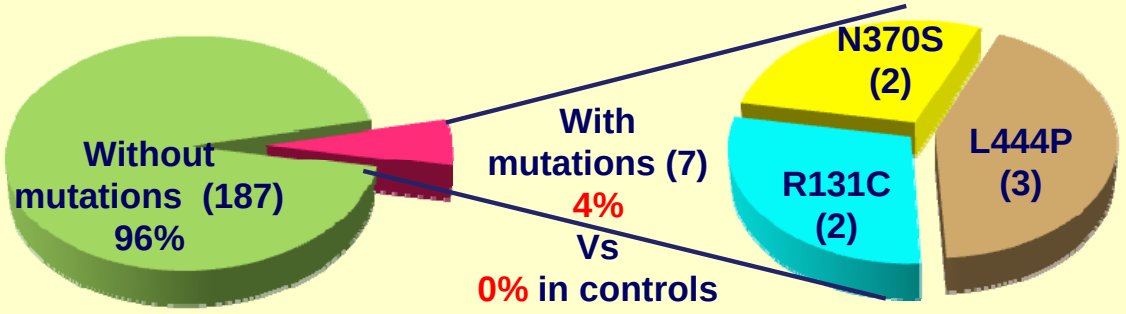
Sidransky *et al,* NEJM, 2009

GBA MUTATIONS IN EUROPEAN PARKINSON'S DISEASE CASES AND CONTROLS



DISTRIBUTION OF GBA MUTATIONS

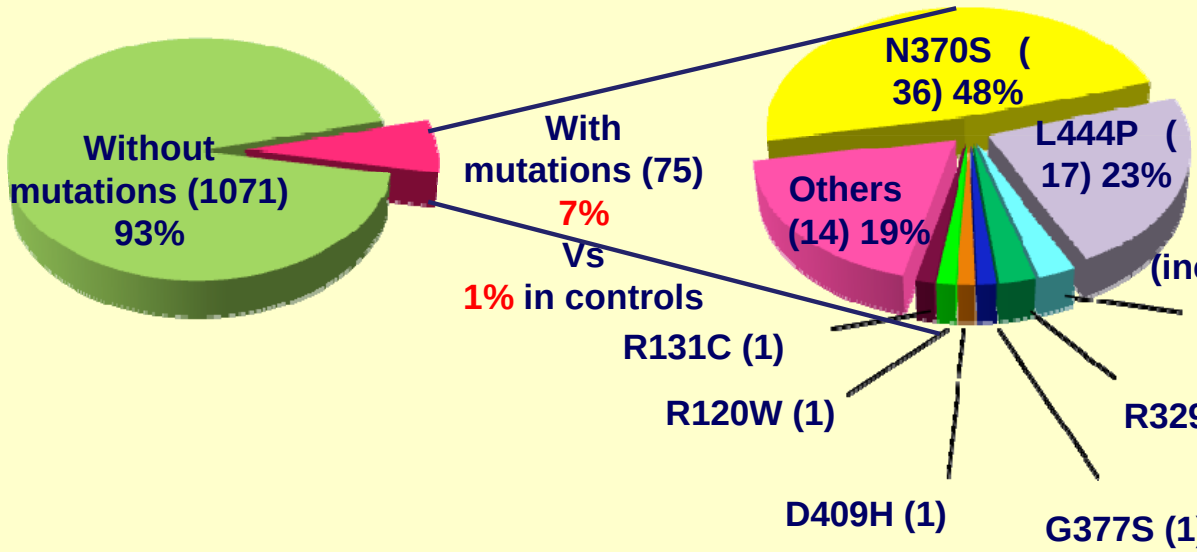
194 North African index cases



p<0,02

(including 2 recombinant alleles)

1146 European index cases



OR=6,78;
CI [2,46-18,66],
p=0,00002

(including 3 recombinant alleles)

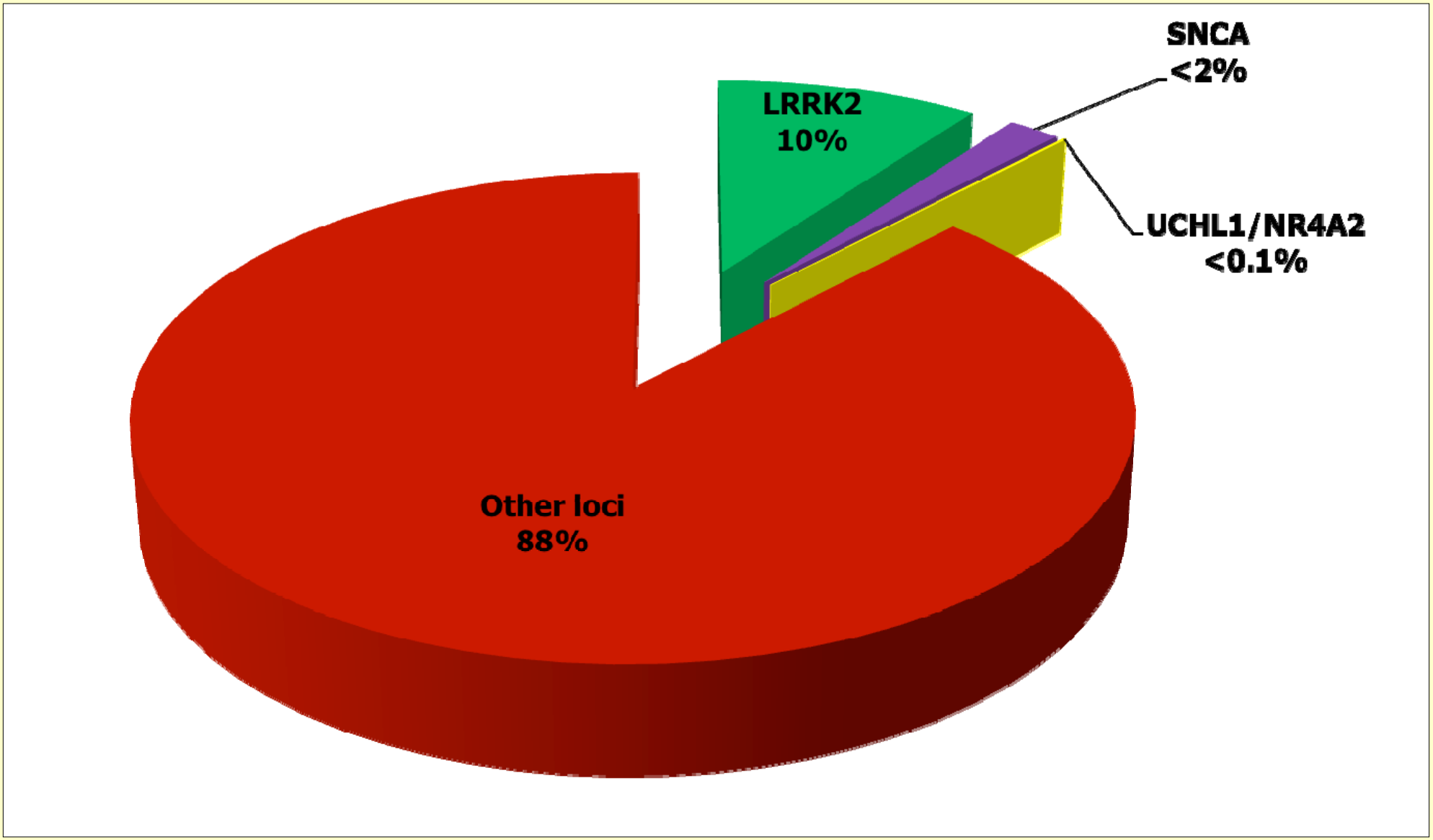
CLINICAL FEATURES OF EUROPEAN PATIENTS WITH PD

	Carriers N=98	**Non carriers** N=1322	
Sex (Males:Females)	51:47	772:550	
Mean age at onset of PD (years)	50,9±12,8	50±13,6	
(range)	(16-73)	(10-86)	
Mean age at examination (years)	59,5±12,4	58,8±13,9	
(range)	(25-85)	(14-90)	
Mean duration of the disease (years)	8,5±5,9	8,7±7,4	
(range)	(0-30)	(0-63)	
Rigidity (%)	92	95	
Bradykinesia (%)	95	97	
Rest tremor (%)	78	74	
Dyskinesia (%)	62	50	p<0,05
Mini-Mental State (/30)	27,6±4,6	28,2±3	

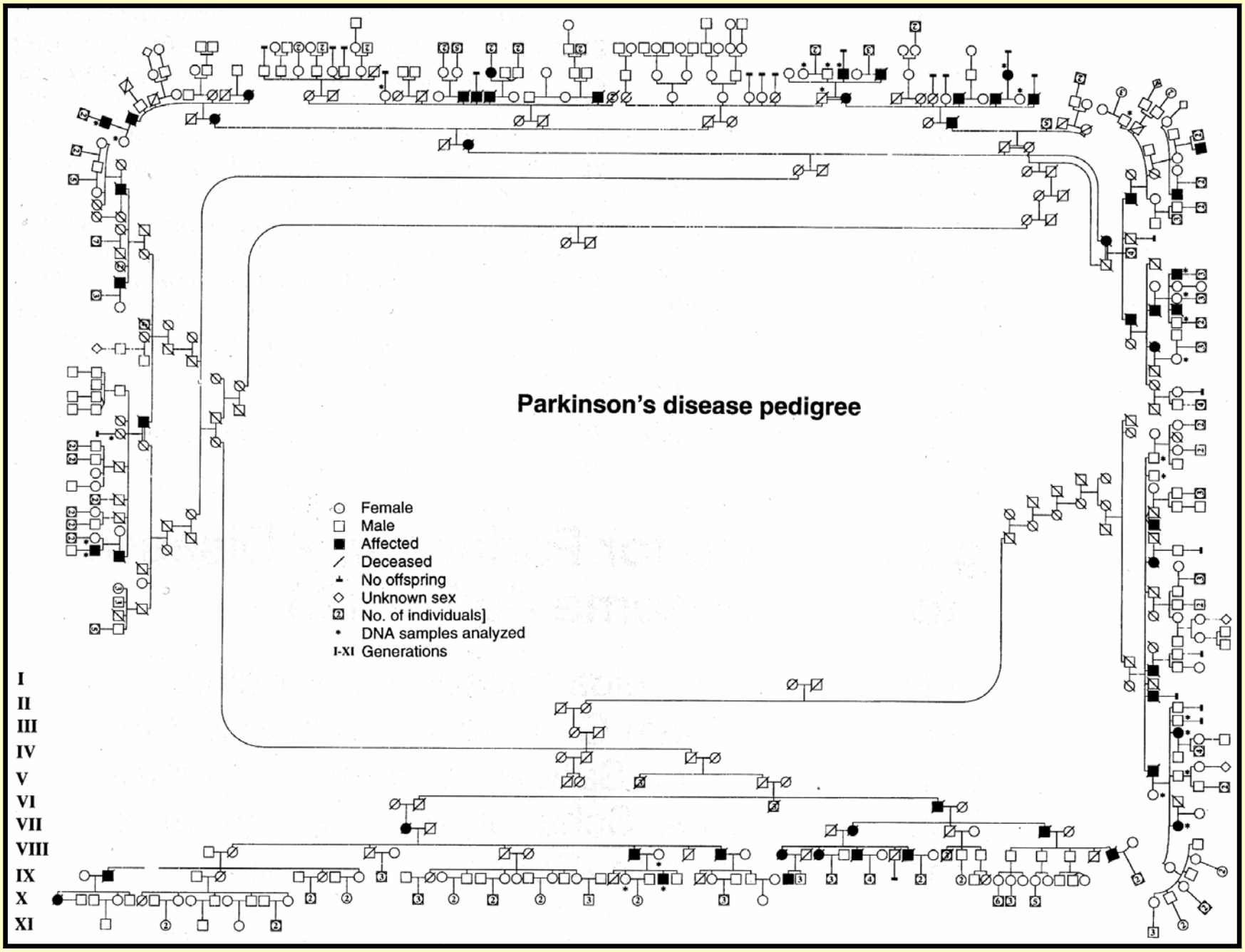
MAIN CHARACTERISTICS OF MONOGENIC FORMS OF PARKINSON'S DISEASE

Designation	Locus	Gene	Transmission	Mean age at onset (years)	Progression	Lewy bodies
PARK1/4	**4q21-33**	**α-synuclein**	**AD**	**Variable**	**Severe**	**+**
PARK2	6q25-2.27	Parkin	AR	Early	Very slow	- (except two cases)
PARK3	2p13	?	AD	Late	Slow	+
PARK5	4p14	UCH-L1	Probable AD	50	?	ND
PARK6	1p35-36	Pink1	AR	Early	Slow	ND
PARK7	1p36	DJ-1	AR	Early	Slow	ND
PARK8	12p11.2-q13.1	LRRK2	AD	Late	?	Variable
PARK9	1q36	ATP13A2	AR	Juvenile	Severe	ND
PARK11	2q36-37	GIGYF2	AD	Late	Severe	ND

AUTOSOMAL DOMINANT FORMS OF PARKINSONISM

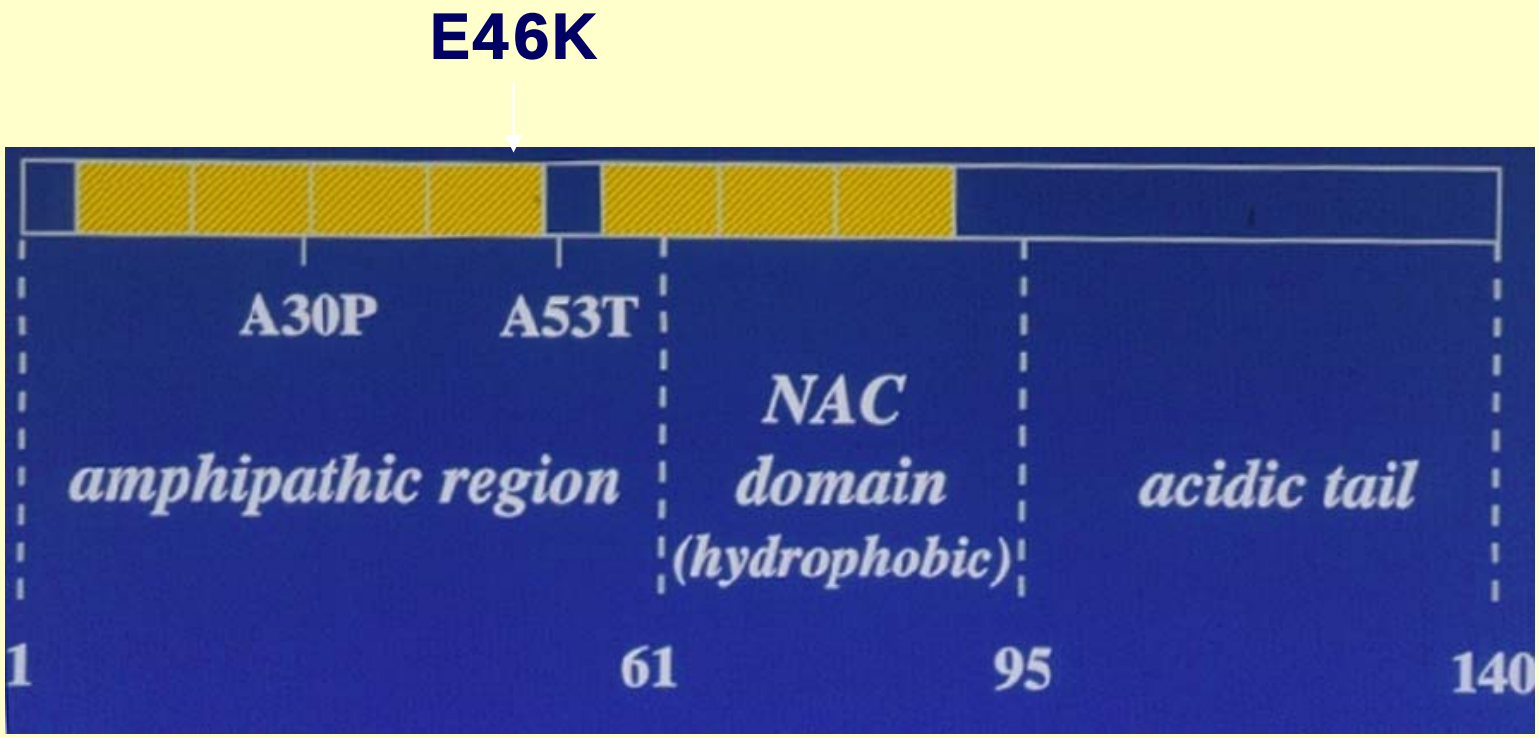


THE CONTURSI KINDRED WITH THE A53T MUTATION IN THE α-SYNUCLEIN GENE

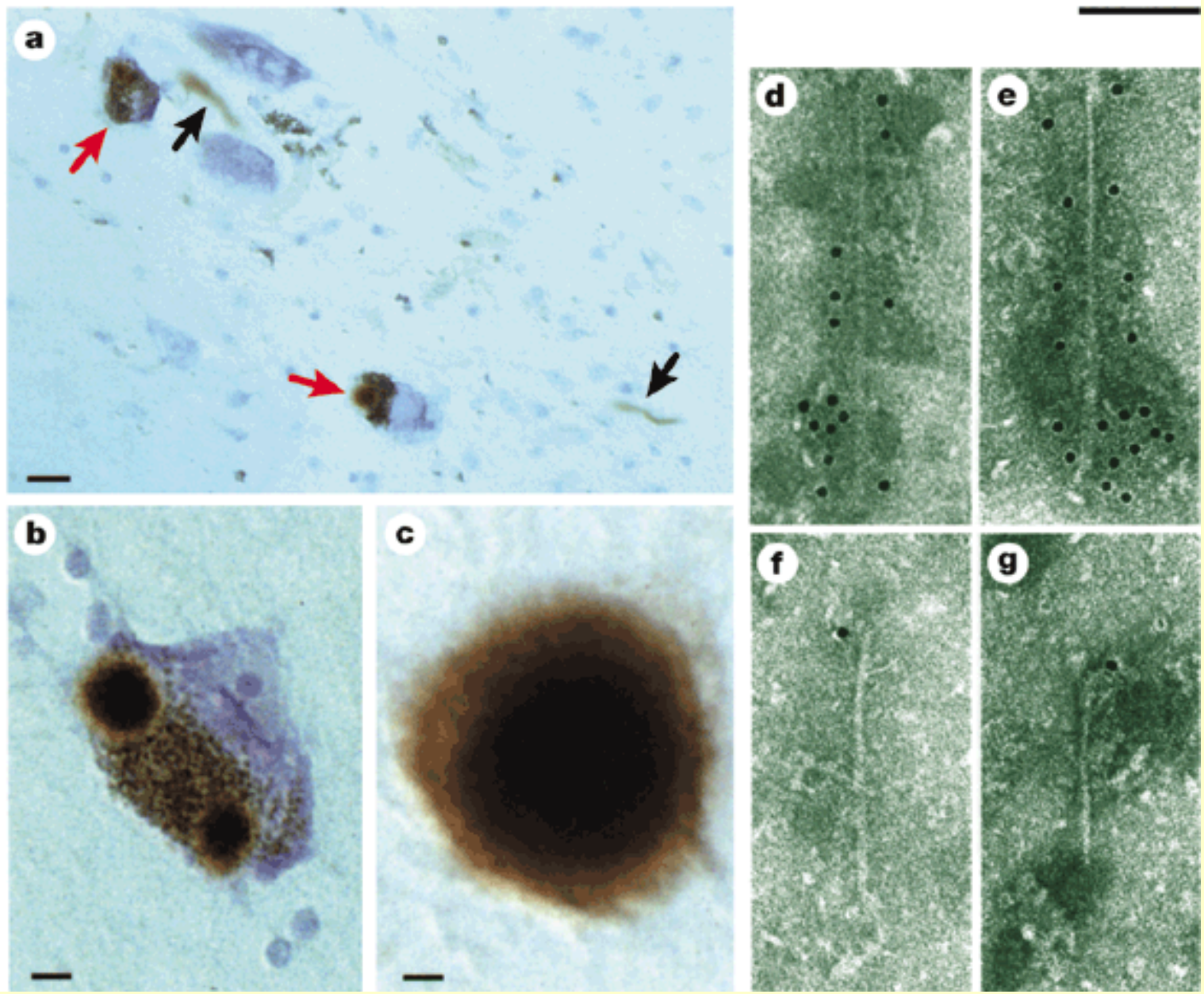


Adapted from Polymeropoulos *et al,* 1996

THE α-SYNUCLEIN PROTEIN

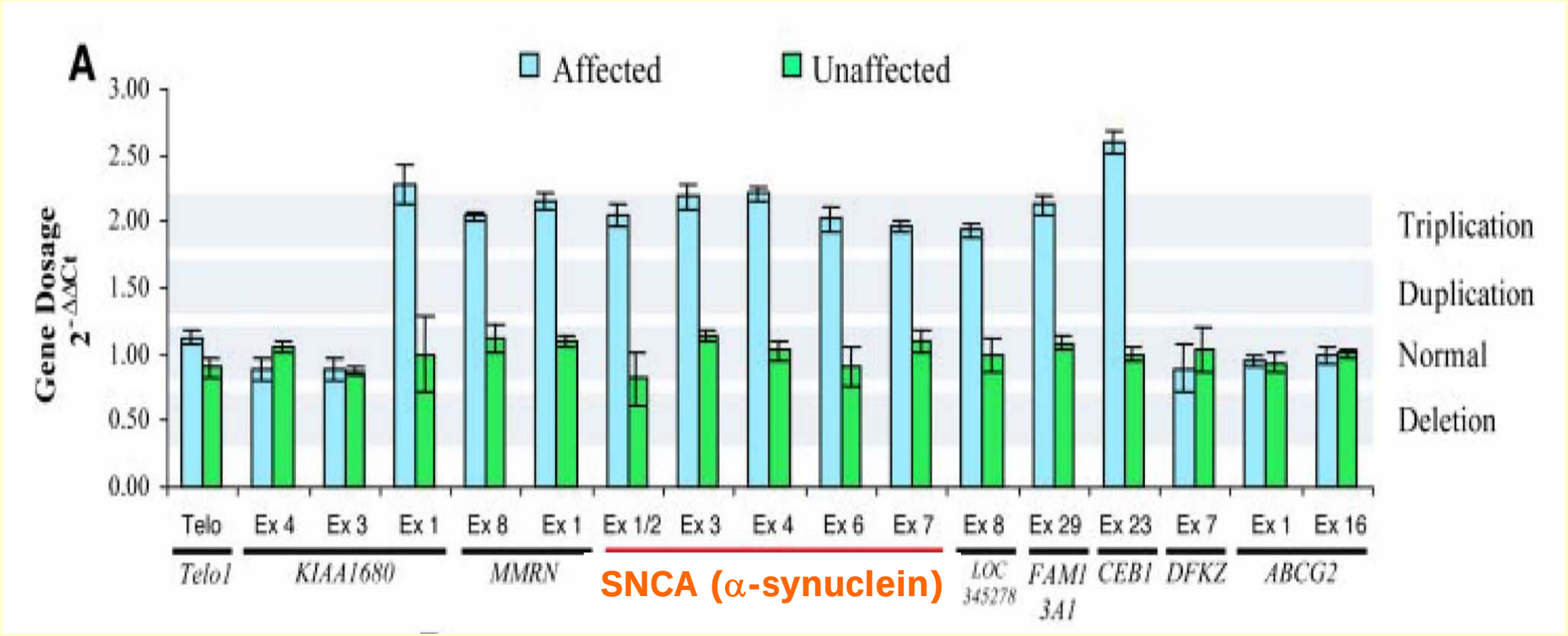


α-SYNUCLEIN PATHOLOGY IN PARKINSON'S DISEASE



Adapted from Goedert, 2001

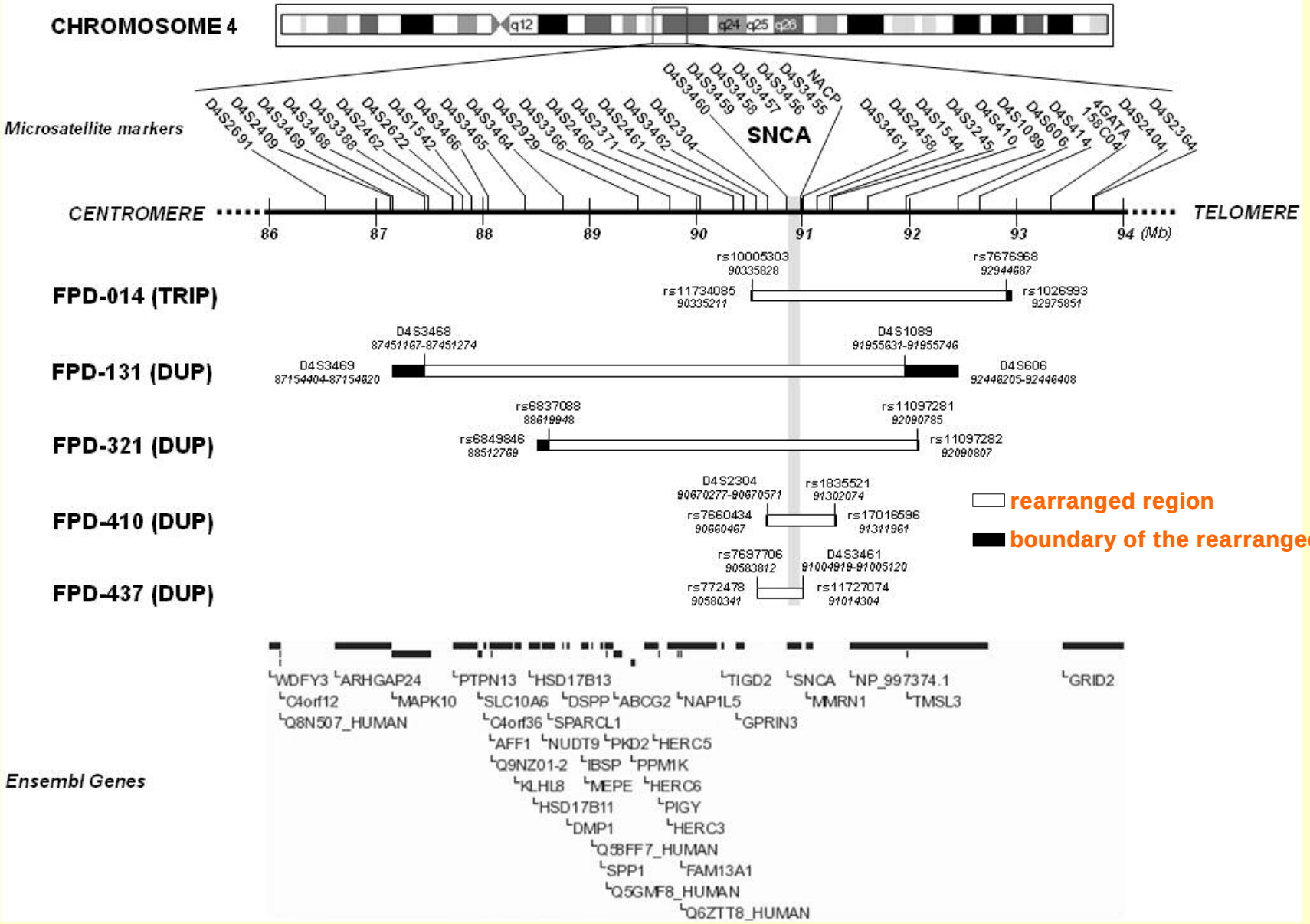
α-SYNUCLEIN LOCUS TRIPLICATION CAUSES AUTOSOMAL DOMINANT PARKINSON'S DISEASE (PARK5)



1.61-2.04 Mb (17 genes)

Singleton *et al*, 2003

DUP- AND TRIPLICATIONS OF THE α-SYNUCLEIN GENE DIFFER IN SIZE



Ibanez *et al*, 2009

FREQUENCY OF α-SYNUCLEIN MULTIPLICATIONS IN FAMILIAL CASES

Population	n	Patients (%)	Reference
Iowa		1	Singleton *et al*, 2003
USA	43	2 (2.4%)	Farrer *et al*, 2004; Fuchs *et al*, 2007
Japan	113	2 (1.8%)	Nishioka *et al*, 2006
Korea	37	1 (2.7%)	Ahn *et al*, 2008
Europe, North Africa	405	6 (1.5%)	Ibanez *et al*, 2009; Ibanez *et al*, 2004; Chartier *et al*, 2004
Japan		1	Ikeuchi *et al*, 2008

α-SYNUCLEIN GENE DOSAGE

	Duplication	n	Triplication	n
Number	26		18	
Age at onset	50 (28-74)	26	41 (20-61)	18
Age at death	65 (48-84)	12	49 (32-62)	3
Disease duration	10 (1-23)	19	9 (6-12)	3
Parkinsonism		19		7
Bradykinesia	100%		100%	
Rigidity	89%		100%	
Rest tremor	53%		86%	
Dementia	23%	20	100%	7
Dysautonomia	20%	5	100%	7

α-SYNUCLEIN AND PARKINSON'S DISEASE

- Missense mutations (A30P, E46K, A53T)	→	Autosomal dominant Parkinson's disease « plus » or dementia with Lewy bodies (early onset)
- Gene triplication (4 copies)	→	Autosomal dominant dementia with Lewy bodies (early onset)
- Gene duplication (3 copies)	→	Autosomal dominant Parkinson's disease (late onset)
- ↑synthesis and/or ↓degradation	→	Idiopathic Parkinson's disease (late onset)

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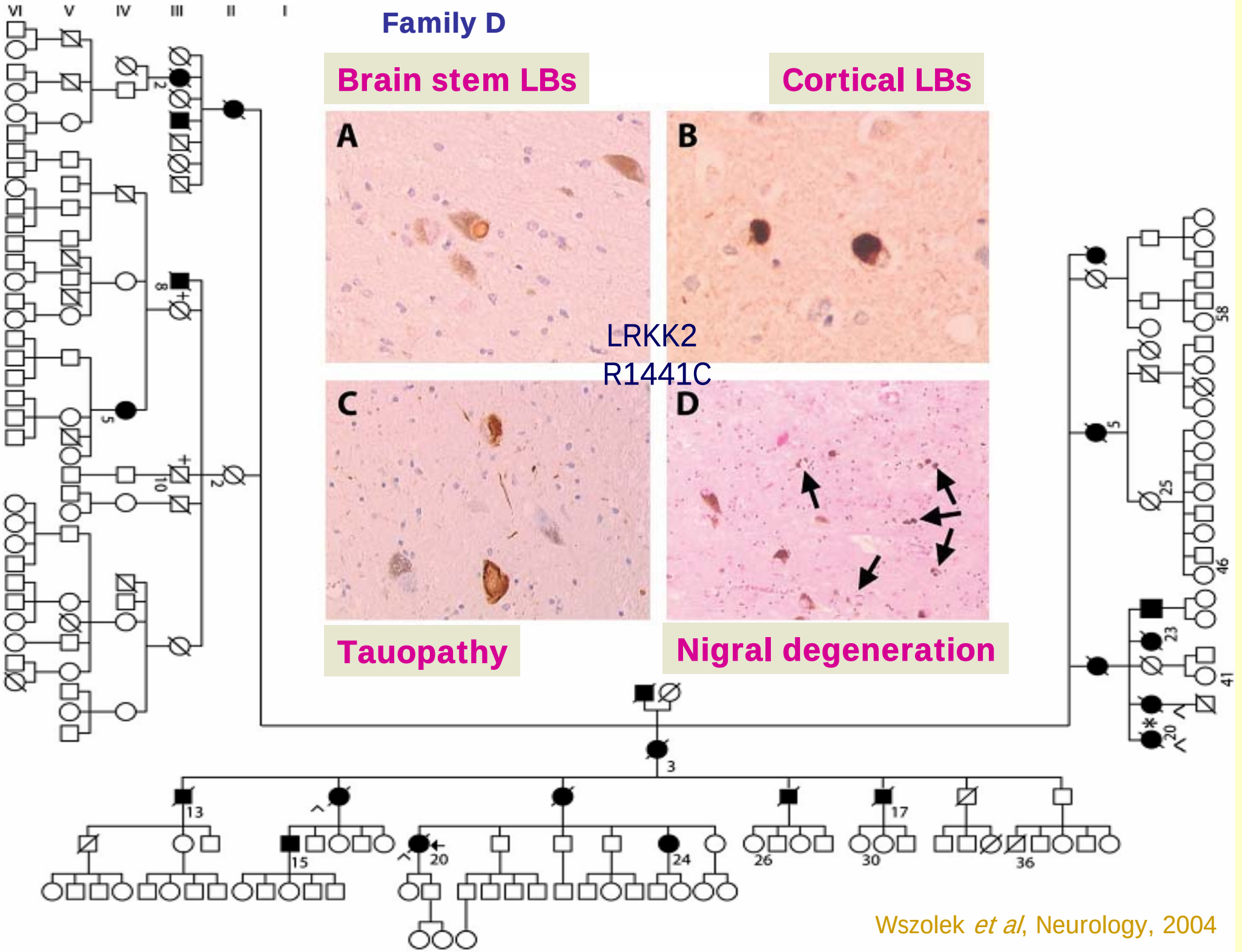
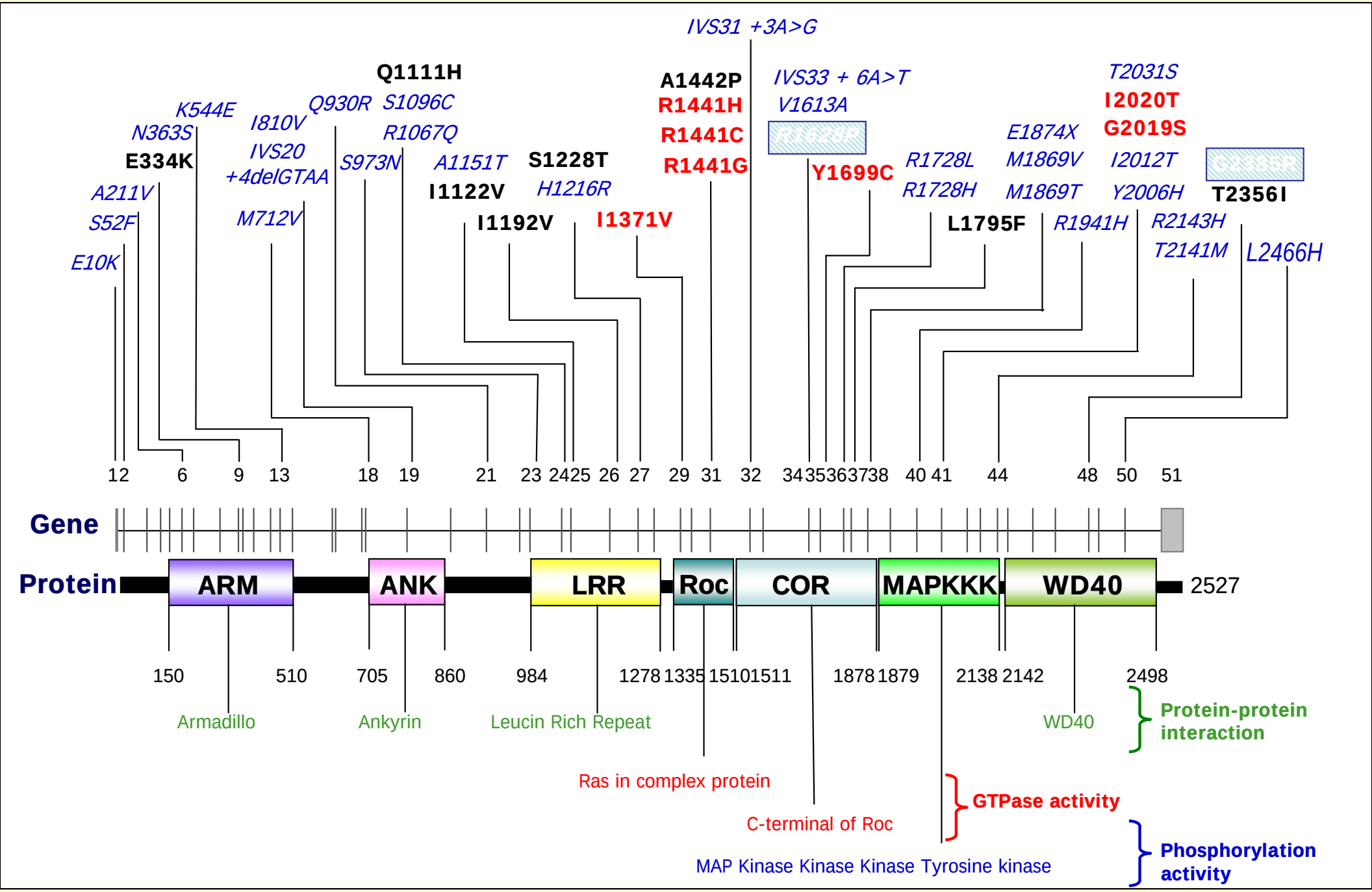
PARK8	**12p11.2-q13.1**	**LRRK2**	**AD**	**Late**	**?**	**Variable**
PARK9	1q36	ATP13A2	AR	Juvenile	Severe	ND
PARK11	2q36-37	GIGYF2	AD	Late	Severe	ND


Family D
Brain stem LBs
Cortical LBs
A
B
LRKK2
R1441C
C
D
Tauopathy
Nigral degeneration
VI
V
IV
III
II
I
Wszolek *et al*, Neurology, 2004

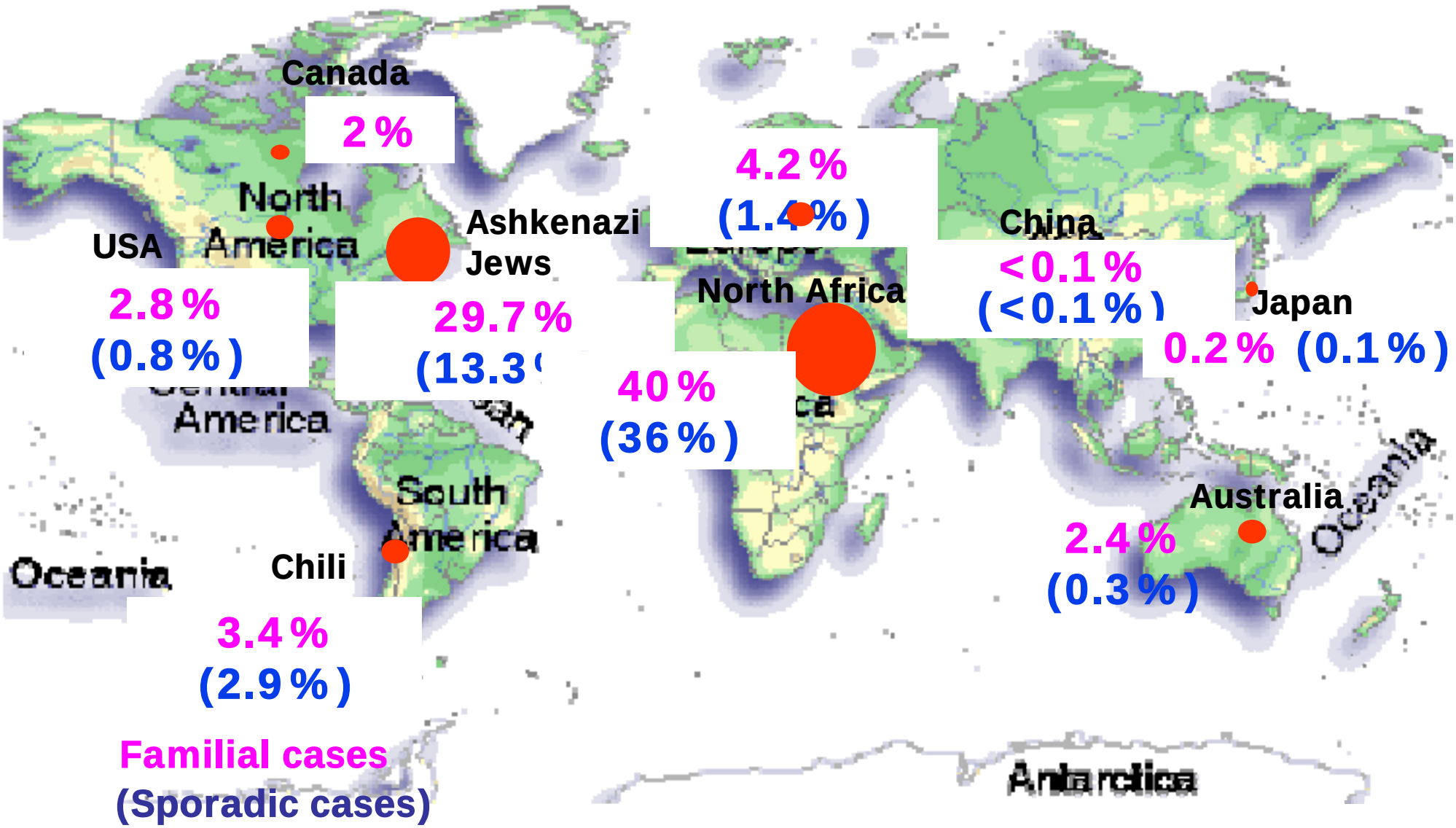
MUTATIONS IN THE LRRK2 GENE



FREQUENCIES OF THE LRRK2 G2019S MUTATION IN FAMILIAL AND ISOLATED PD CASES FROM NORTH AFRICA

	Previous study *Lesage et al, NEJM, 2006*	Present study *Lesage et al, Neurology, 2009*	Combined studies
Familial PD (%)	10/27 (37%) (1 homozygote)	7/17 (41%) (1 homozygote)	17/44 (39%) p<0.001
Isolated PD (%)	20/49 (41%) (2 homozygotes)	40/119 (34%) (2 homozygotes)	60/168 (36%) p<0.001
Controls (%)	2/151 (1%)	1/66 (1.5%) (1 homozygote)	3/217 (1%)

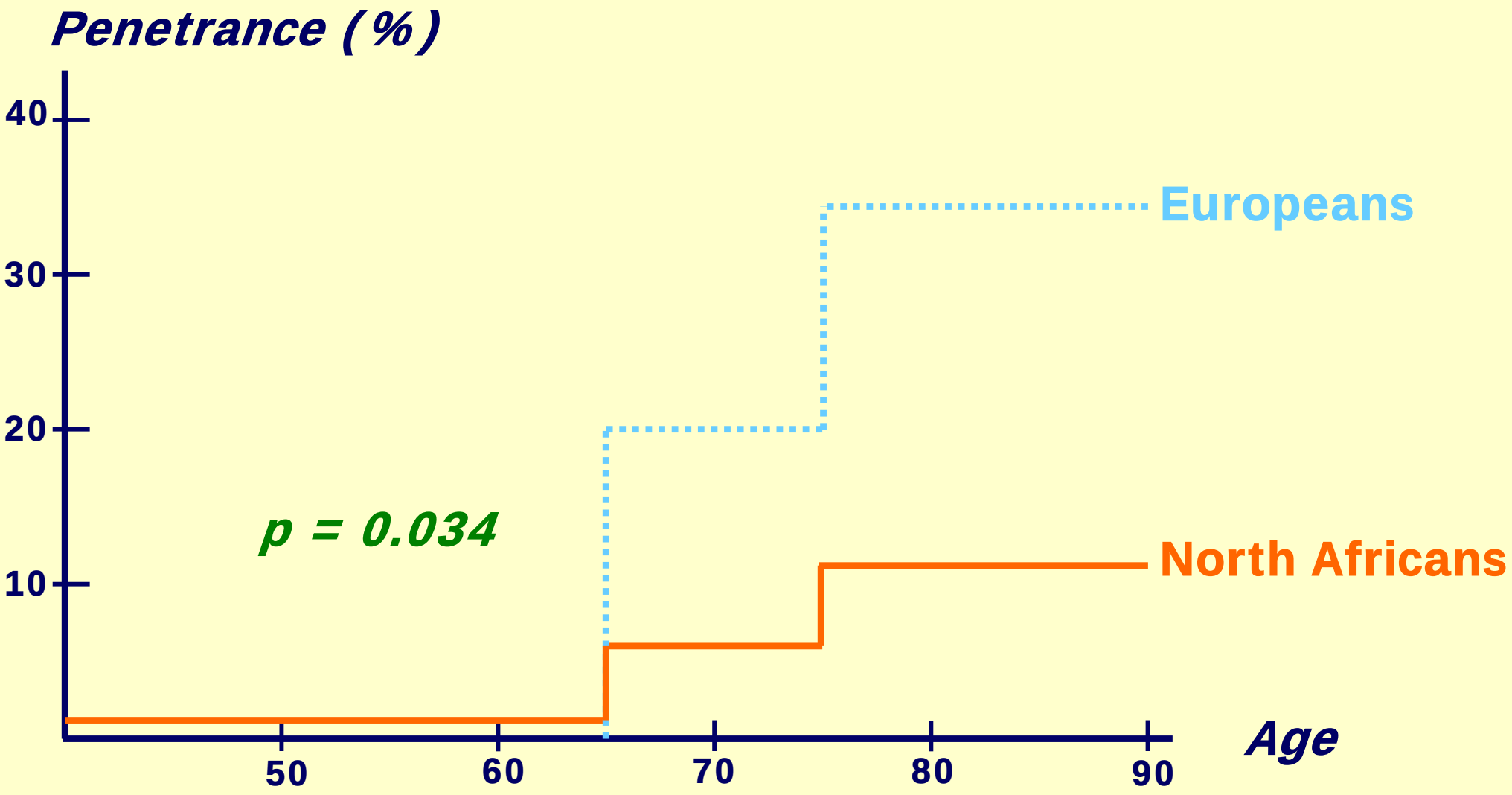
WORLDWIDE DISTRIBUTION OF THE LRRK2 G2019S MUTATION



Estimation of the penetrance of the G2019S mutation

			Cumulative Penetrance (%)				
Population /Country	**Probands (G2019S)**	**N**	**6th decade**	**7th decade**	**8th decade**	**9th decade**	**Reference**
North America/ Asia/ Europe	7	34	22	68	85		Kachergus, 2005
Ashkenazi Jews (US)	22	44				31.8	Ozelius, 2006
North America	28		7	12	18	24	Clark, 2006
Italy	19	51		15	21	32	Goldwurm, 2007
Multiple	327	1045	28	51	74		Healy, 2008
North African	72	609			45		Hulihan, 2008
North Africa/ Europe	57	315	1	12	20	20	Troiano, 2008

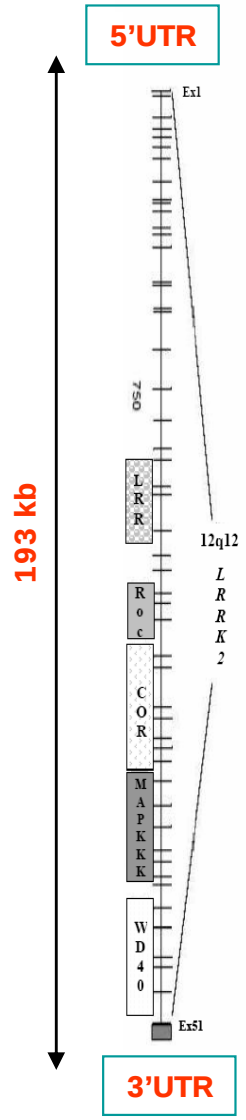
PENETRANCE OF THE G2019S MUTATION ACCORDING TO THE GEOGRAPHICAL ORIGIN



Troiano *et al,* 2008

EXISTENCE OF THREE G2019S-CONTAINING HAPLOTYPES

Markers	Physical map	755-004	357-008	314-015	750-001	025-016	292-001	729-005	583-012	163-013	6047	Haplotype 1	030-010	497-007	Haplotype 2	1107	013-001	Haplotype 3
D12S9AG	38863278	178	178	178	178	178	178	178	178/172	178	178	178	178	178/172	178	178	178	178
D12S2514	38873924	291	291	291	291	291	291	291	291/294	291	291	291	291	291	291	294	294/291	294
rs28903073	38939777	A	A/G	A/G	A/G	A/G	A/G	A	A/G	A/G	A/G	A	G	G	G	G	G	G
D12S9AT	38973965	293	293	293/295	293/297	293	293	293	293	293	293/295	293	293	293	293	295	295/293	295
rs7966550	38974962	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
D12S2516	38989339	254	254	254/252	254	254	254/252	254	254	254	254/252	254	254	254	254	252	252/254	252
rs1427263	39000101	A	A	A/C	A	A	A/C	A	A	A	A/C	A	A	A	A	C	C/A	C
rs11176013	39000140	G	G	G/A	G/A	G	G/A	G	G	G	G/A	G	G	G	G	A	A/G	A
rs11564148	39000168	A	A/T	A/T	A/T	A	A/T	A	A	A	A/T	A	A	A	A	T	T	T
rs2404834	39015274	C	C	C	C/T	C	C	C	C	C	C	C	T	T	T	C	C	C
rs7302841	39015923	A	A/G	A/G	A/G	A	A/G	A	A	A	A/G	A	G	G	G	G	G	G
A>C	39017449	A	A	A	A/C	A	A/C	A	A	A	A	A	C	C	C	A/C	A	A
rs715402	39017481	A	A	A/G	A	A	A	A	A	A	A/G	A	A	A	A	A/G	A/G	A
rs6581667	39017773	C	C	C/G	C/G	C	C/G	C	C	C	C/G	C	G	G	G	G	G/C	G
G>A	39017873	A	A	A/G	A/G	A	A/G	A	A	A	A/G	A	G	G	G	G	G/A	G
G2019S	39020469	A	A/G	A/G	A/G	A	A/G	A	A/G	A/G	A/G	A	A	A	A	A/G	A/G	A
rs10506155	39022206	G	G	G	G/A	(G)	G/A	G	G	G	G	G	A	A	A	G/A	G	G
A>G	39022277	G	G	G/A	G	(G)	G	G	G	G	G/A	G	G	G	G	G/A	G/A	G/A
T>A	39022310	A	A	A/T	A	(A)	A	A	A	A	A/T	A	A	A	A	A/T	A/T	A/T
rs919714	39022516	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C/T	C
rs10784522	39026632	T	T/G	T/G	T/G	T	T/G	T	T	T	T/G	T	G	G	G	G	G	G
rs10878405	39028521	A	A/G	A/G	A/G	A	A/G	A	A	A	A/G	A	G	G	G	G	G	G
D12S2518	39034922	154	154	154/168	154	154	154	154	154	154	154/168	154	154	154	154	154/168	154/168	154/168
ss52051244	39043597	A	A	A	A/G	A	A/G	A	A	A	A	A	G	G/A	G	A	A/G	A
D12S8TA	39056001	154	154/152	154/152	154	154	154/152	154	154/156	154/156	154/152	154	154/152	154/152	154/152	152	152	152
		France	Portugal	The Netherlands	North USA	Jews (Algeria)	Jews (France)	Algeria	Morocco	Tunisia	South Africa		France	France		Japan	France	

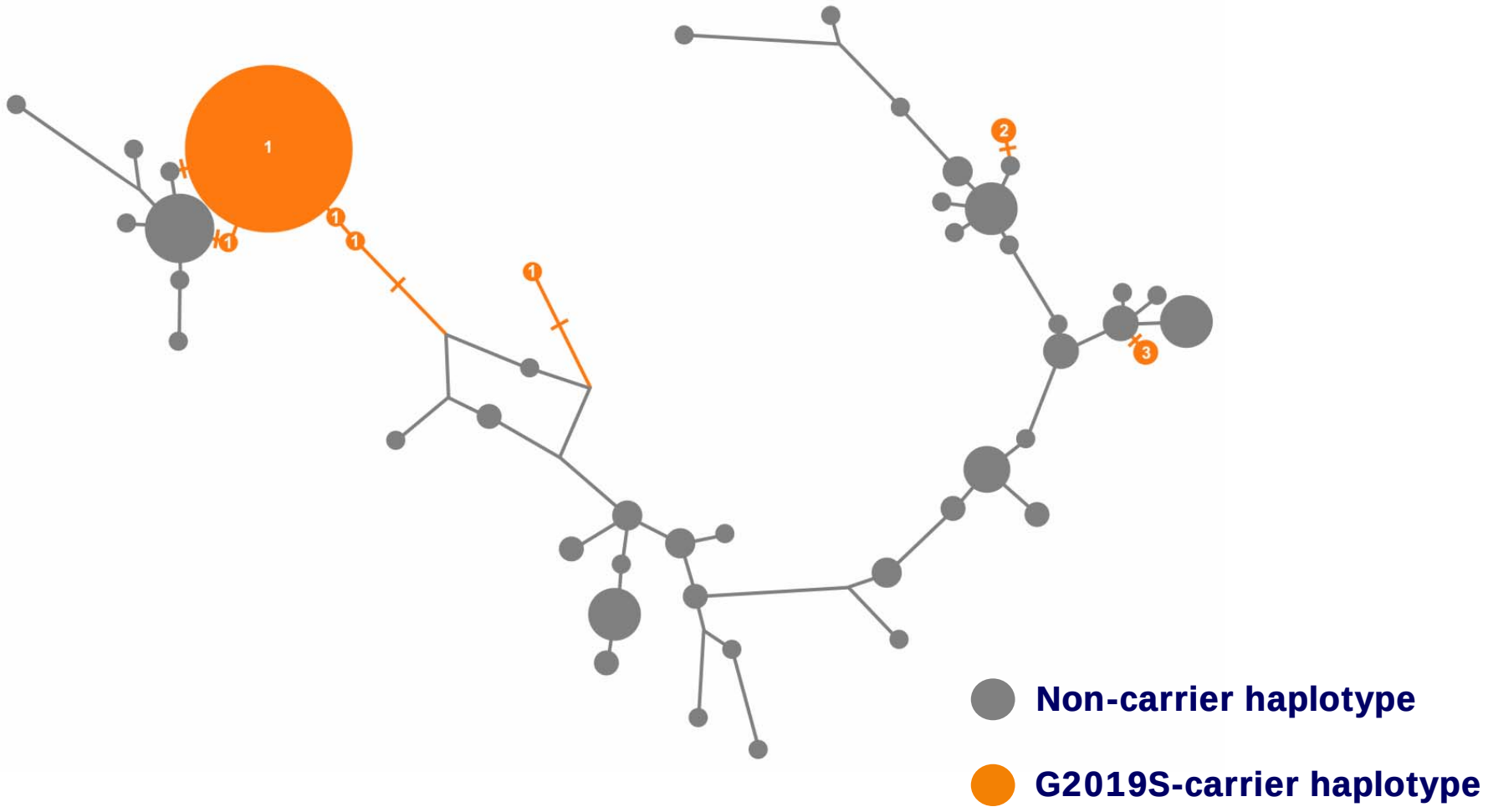


Hap1: 95% (Europeans, North and South Africans and Jews)

Hap2: 2% (Europeans)

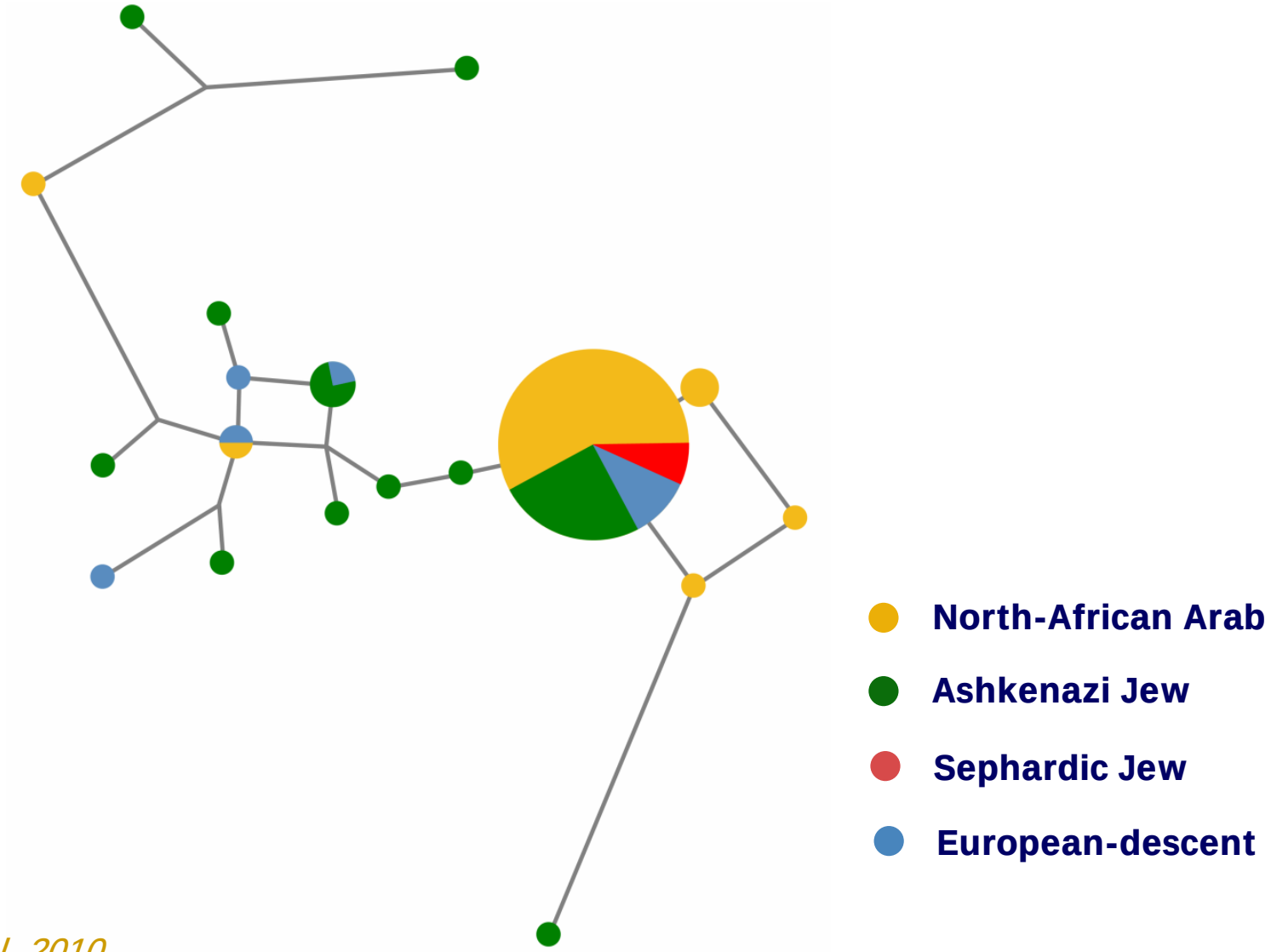
Hap3: 3% (Asians)

HAPLOTYPE NETWORK OF THE LRRK2 G2019S CORE REGION



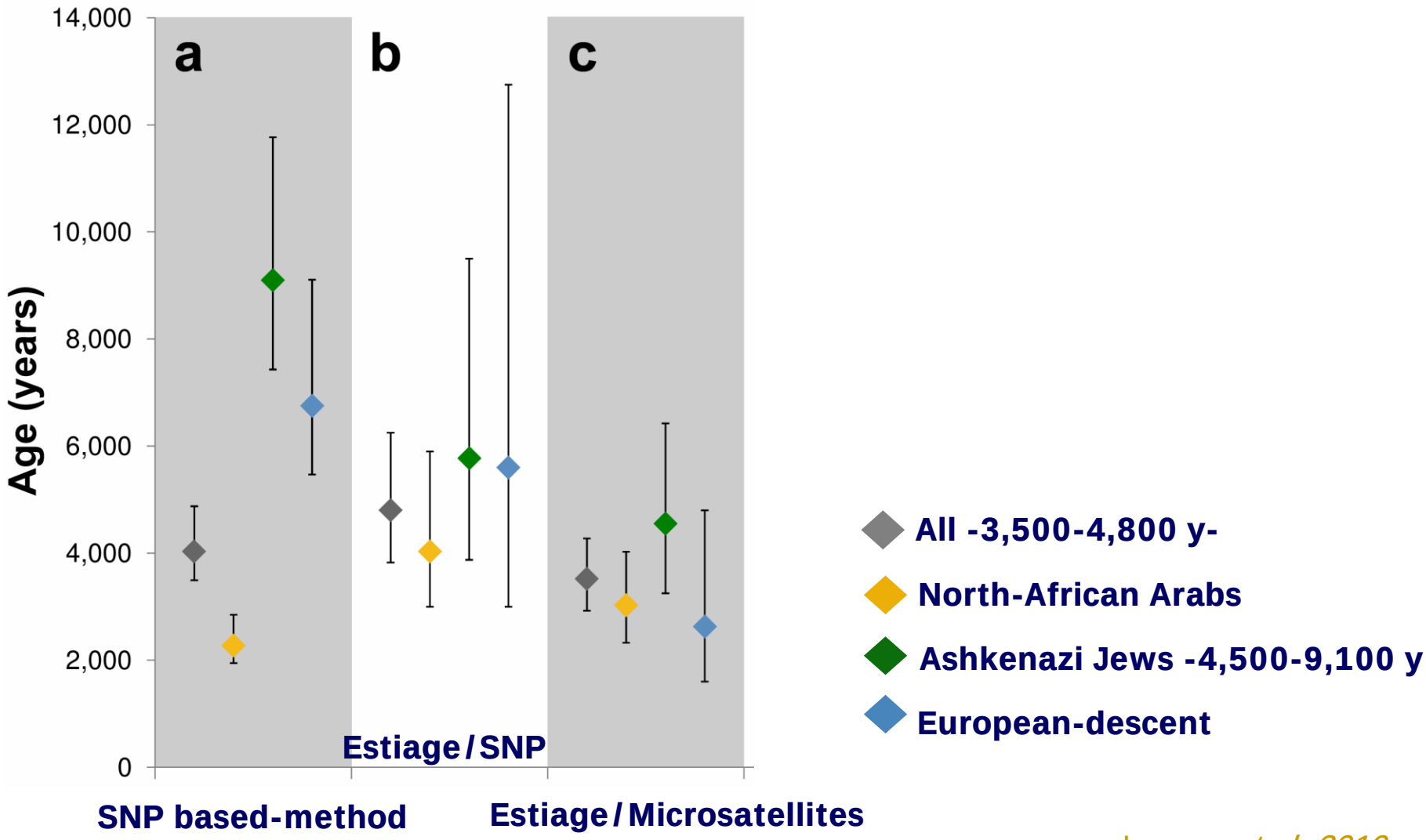
Lesage *et al, 2010*

HAPLOTYPE NETWORK OF THE G2019S-CARRYING HAPLOTYPE 1



Lesage *et al, 2010*

AGE OF THE G2019S MUTATION IN THREE ETHNIC GROUPS WITH DIFFERENT METHODS



Lesage *et al, 2010*