Programmi in rete dei centri di eccellenza
dell'area neurologica-riabilitativa

9 febbraio 2006

Epidemiologia genetica del parkinsonismo familiare

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Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute

Istituto Superiore di Sanità

I SEI QUESITI DELL'EPIDEMIOLOGIA CLINICA NEL CONTESTO DELLA GENETICA DELLA MALATTIA DI PARKINSON

- **1. DIAGNOSI – Necessità di effettuare una diagnosi su base genetica di alcune forme di parkinsonismo**

- **2. FREQUENZA - Quanto sono frequenti le forme parkinsoniane su base genetica ?**

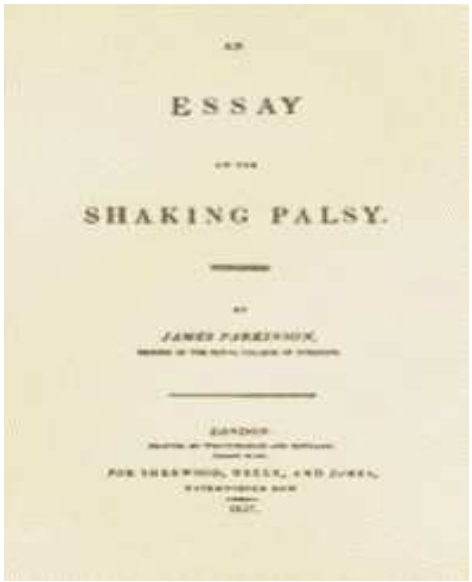
- **3. RISCHIO – Quali fattori sono associati ad una maggiore penetranza della malattia (correlazioni fenotipo-genotipo)**

- **4. PROGNOSI – Quali sono le conseguenze derivanti dall'essere affetti da un parkinsonismo genetico ?**

- **5.TRATTAMENTO – Come cambia un trattamento il decorso del parkinsonismo su base genetica?**

- **6. PREVENZIONE – Quando effettuare un test genetico**

LA FAMILIARITA'
PER MALATTIA DI PARKINSON



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

EPIDEMIOLOGIA DESCRITTIVA DELLA MALATTIA DI PARKINSON

INCIDENZA 4.5 – 23 casi per 100.000 ab/anno

PREVALENZA 67- 250 casi per 100.000 ab.

MORTALITA' 1- 6 casi per 100.000 ab.

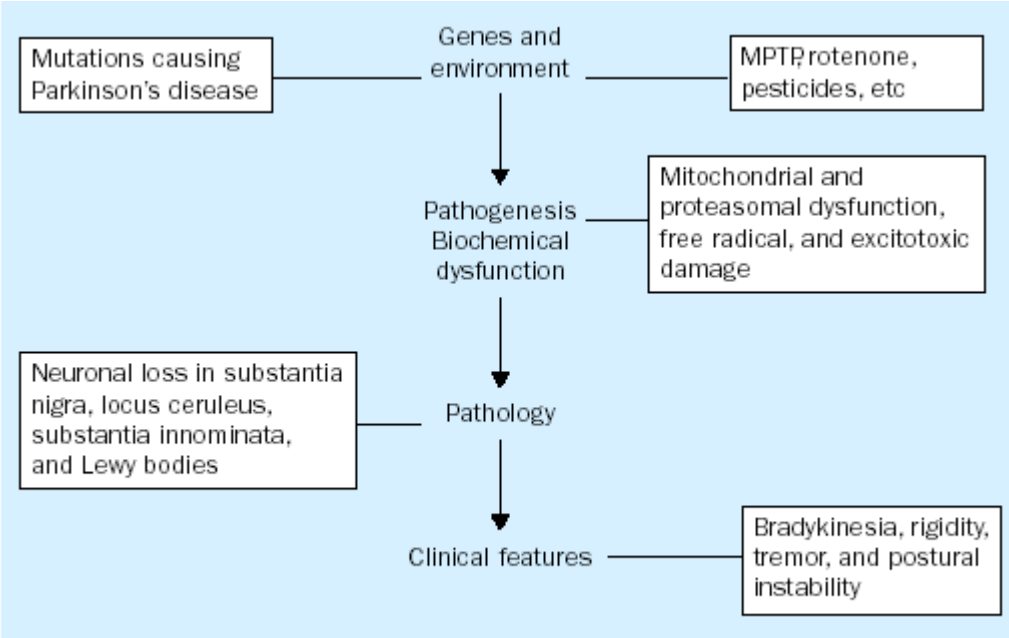


Figure 1. Aetiology and pathogenesis of PD.

Lancet Neurol 2004; **3:** 362–68

Anthony HV Schapira

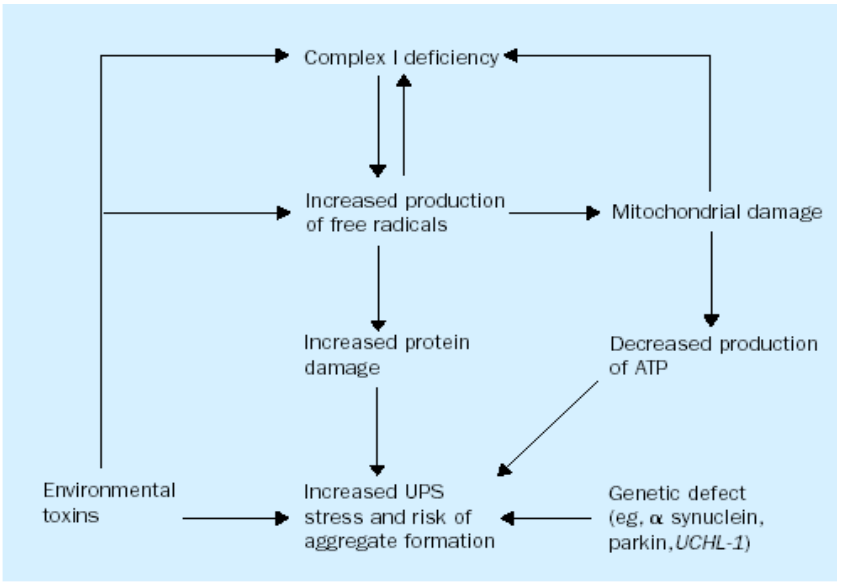
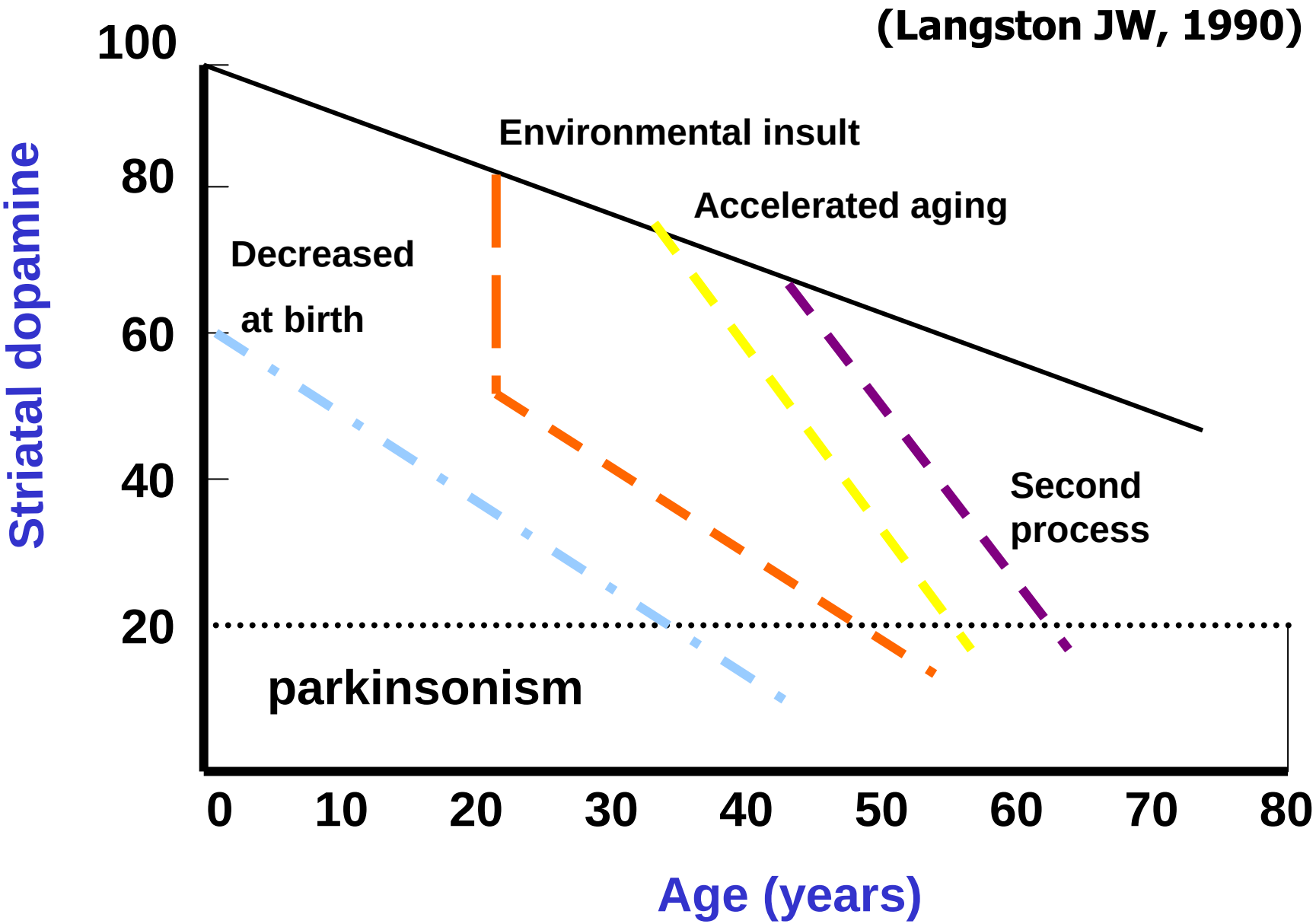
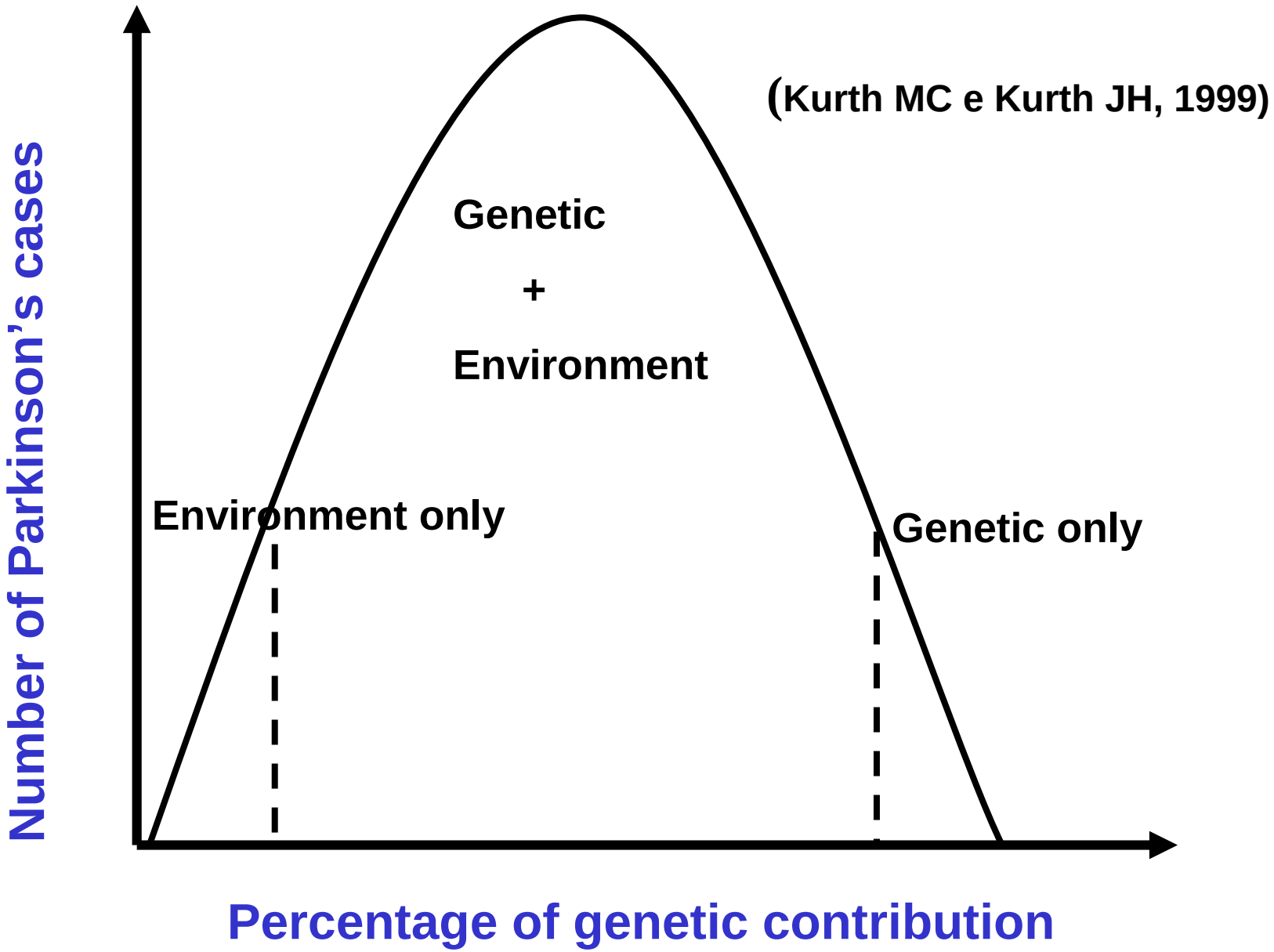


Figure 2. Interacting pathogenetic factors in PD.


(Langston JW, 1990)
Striatal dopamine
100
80
60
40
20
Environmental insult
Accelerated aging
Decreased
at birth
Second
process
parkinsonism
0
10
20
30
40
50
60
70
80
Age (years)


(Kurth MC e Kurth JH, 1999)
Genetic
+
Environment
Environment only
Genetic only
Number of Parkinson's cases
Percentage of genetic contribution

Acta Neurol Scand 1995: 92: 49–54
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Estimate of parkinsonism prevalence through drug prescription histories in the Province of Rome, Italy

Menniti-Ippolito F, Spila-Alegiani S, Vanacore N, Bonifati V, Diana G, Meco G, Raschetti R. Estimate of parkinsonism prevalence through drug prescription histories in the Province of Rome, Italy
Acta Neurol Scand 1995: 92: 49–54. © Munksgaard 1995.

Introduction – The objective of the study was to estimate the prevalence of parkinsonism in the Province of Rome using antiparkinsonian prescription histories from 1986 to 1991. *Methods* – A subject was defined as a case of parkinsonism if he/she had received "specific" and "consistent" antiparkinsonian therapy in the study period. *Results* – In November 1990, 6,572 patients were defined as prevalent cases of parkinsonism. The crude prevalence ratio, for the total population of the Province of Rome, is 173.5 per 100,000 inhabitants (165.9 per 100,000 in men and 180.5 per 100,000 in women). The method was validated by record-linkage with clinical records of all patients visited during 1990 at the Department of Neurological Sciences of the University of Rome "La Sapienza". The sensitivity of the prevalence study was 83.6%. *Conclusions* – The use of a computerized data base of all prescription data, routinely collected for administrative purposes, enabled us to obtain a prevalence estimate based on a very large population, with low costs and in a relatively short time.

F. Menniti-Ippolito [1], S. Spila-Alegiani [1], N. Vanacore [2], V. Bonifati [2], G. Diana [3], G. Meco [2], R. Raschetti [1]

Departments of [1] Epidemiology and Biostatistics, [3] Pharmacology Istituto Superiore di Sanità, [2] Neurological Sciences, "La Sapienza" University, Rome, Italy.

Key words: parkinsonism; prevalence; drug prescription data bases; pharmacoepidemiology.

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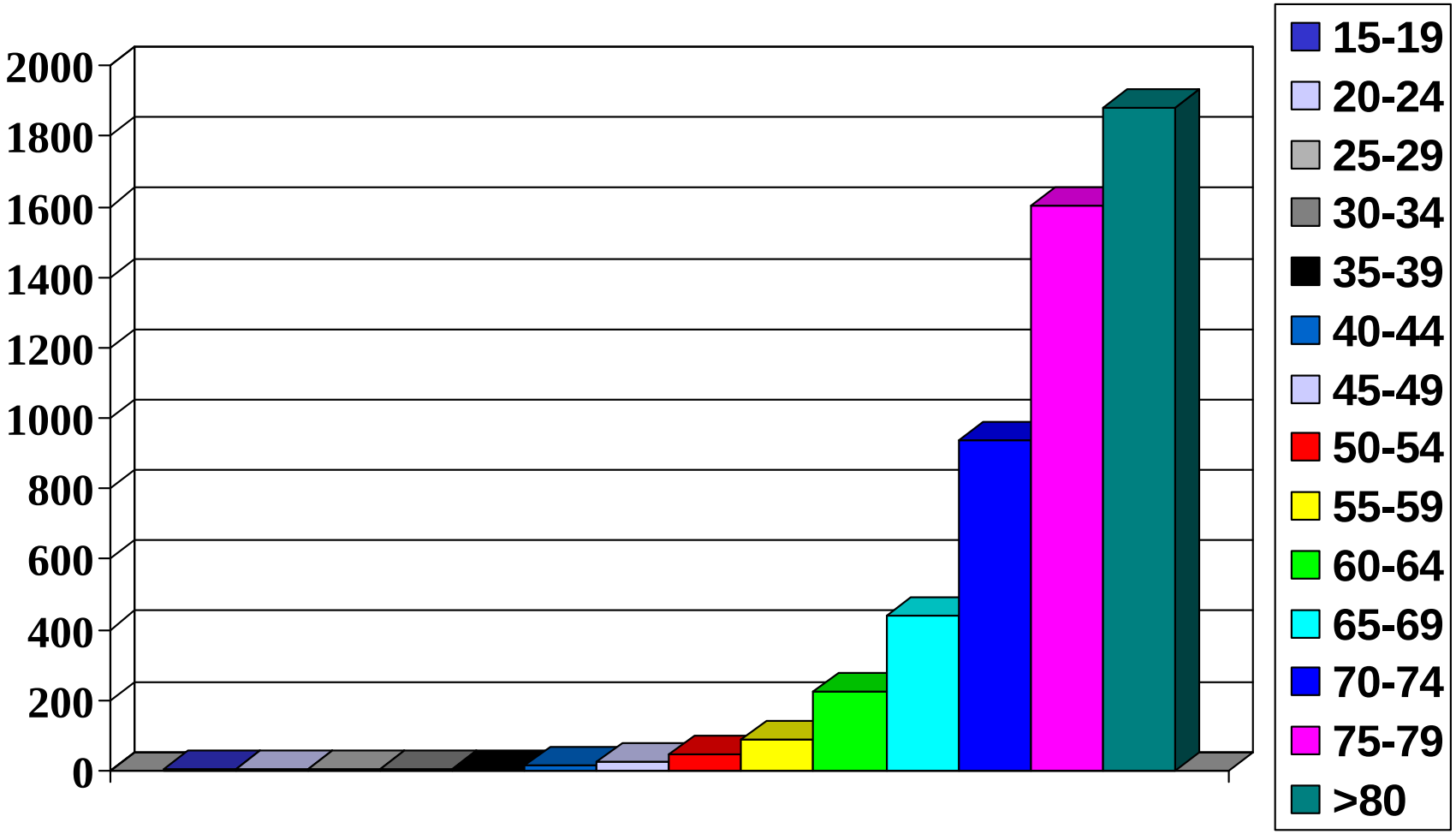
Accepted for publication October 4, 1994

EPIDEMIOLOGIA DELLA MALATTIA DI PARKINSON

(STUDI DI PREVALENZA X 100.000 ab.)



Familial Parkinson's Disease: A Clinical Genetic Analysis

Vincenzo Bonifati, Edito Fabrizio, Nicola Vanacore, Michele De Mari and Giuseppe Meco

ABSTRACT: ***Objective:*** To study the frequency, clinical features and clinical genetics of familial Parkinson's disease (PD). ***Methods:*** Family history for PD and tremors was studied in 100 consecutive PD cases. Spouses served as controls. Clinical features were compared between personally verified familial and sporadic PD cases, from the same consecutive clinical series. Clinical genetic analysis was performed in a larger group of non-consecutive multicase PD families. ***Results:*** Family history for PD was positive in 24% of consecutive PD cases and in 6% of spouse controls ($p < 0.001$). When family history for isolated tremor is also considered, the number of positive cases rises to 43% compared with 9% in controls ($p < 0.001$). Nine of the consecutive cases had at least one living affected relative, for a total of 20 familial PD cases. These familial cases showed an earlier onset age when compared with sporadic ones from the same consecutive series. Within 22 non-consecutive PD families with at least two living and personally examined PD cases (total 52 PD cases), the crude segregation ratios were similar for parents and siblings and the lifetime cumulative risks approached 0.4 in siblings and tended to be comparable, but at later ages, in parents. Ancestral relatives were all unilaterally distributed. In some families, anticipation of onset age in new generations was observed. ***Conclusions:*** The frequency of positive family history for PD and for PD and tremor is higher among PD cases than controls. Familial and sporadic PD only differ in onset age. The clinical genetic analyses support autosomal dominant inheritance with strongly age-related penetrance as most likely in familial PD.

Table 1: Frequencies of positive family histories for PD or tremor in 100 consecutively seen cases and controls.

	Family history for PD only		Family history for PD or tremor	
	Cases	**Controls**	**Cases**	**Controls**
Yes	24 (%)	6 (%)	43 (%)	9 (%)
No	76 (%)	94 (%)	57 (%)	91 (%)
Total	100	100	100	100
	$\chi^2 = 11.333$, $p < 0.001$		$\chi^2 = 28.300$, $p < 0.001$	
	Odds ratio = 4.95 95% c.i. = 2.05 - 11.94		Odds ratio = 7.63 95% c.i. = 3.67 - 15.79	

STUDI SULLA FAMILIARITA' PER MALATTIA DI PARKINSON

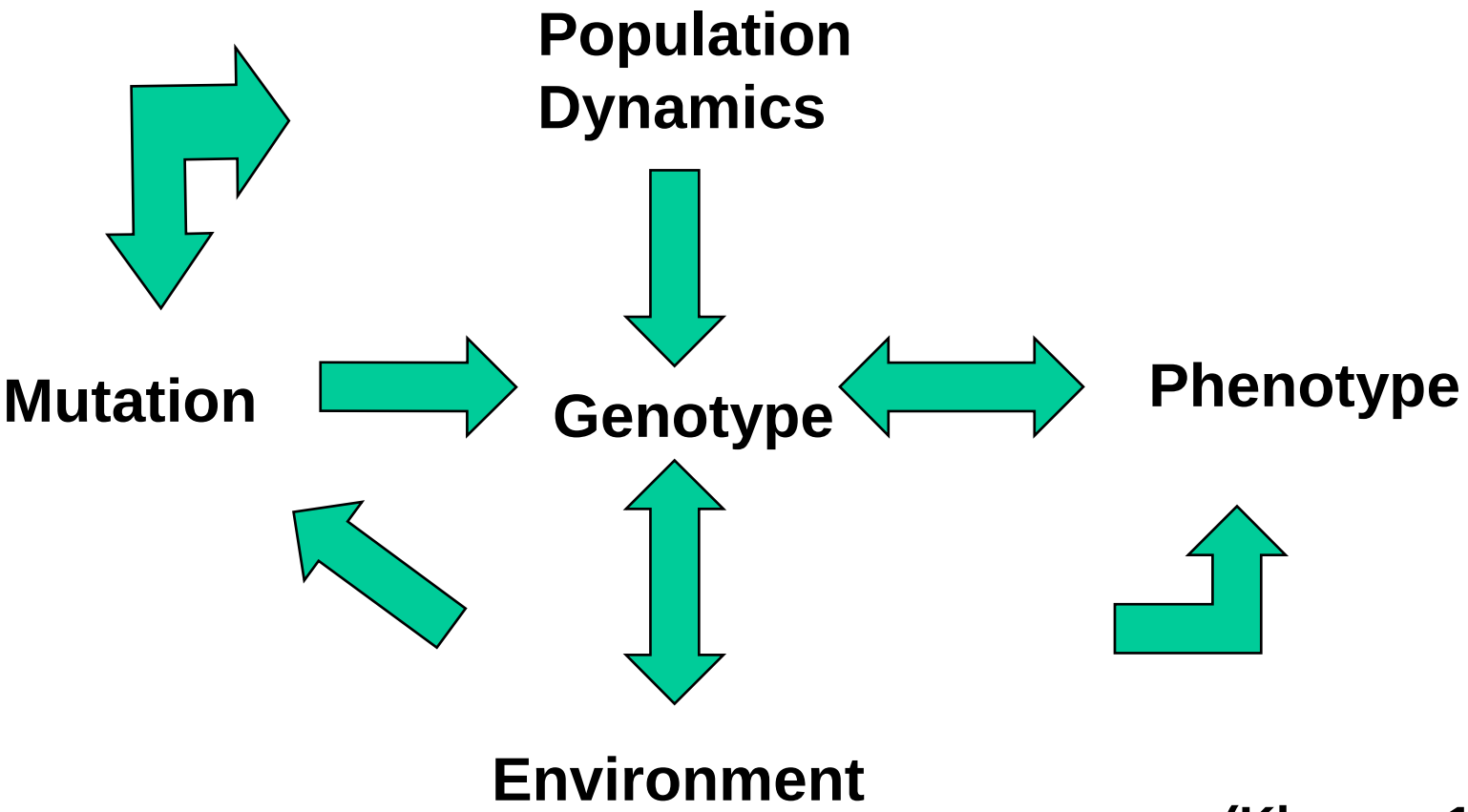
Autore	Casi	Controlli	OR (IC95%)
Semchuch	128	256	2.4 (1-5.4)
Hubble	63	75	2.8 (1.1-7.2)
Butterfield	63	68	3.0 (1.1-8.7)
Payami	114	114	3.5 (1.3-9.4)
Bonifati	100	100	4.9 (2.0-11.9)
Marder	233	1172	2.3 (1.3-4)
De Michele	116	116	14.6 (7.2-29.6)
Elbaz	175	481	3.2 (1.6-6.6)
Taylor	140	147	6.1 (2.3-15.6)
Rybicki	144	464	4.2 (2.3-7.6)
Autere	268	210	2.9 (1.3-6.4)

- **CIRCA IL 15-20% DEI CASI DI MALATTIA DI PARKINSON SONO CASI FAMILIARI**

- **SI STIMA CHE UN PAZIENTE PARKINSONIANO HA UNA PROBABILITA' 2-4 VOLTE MAGGIORE RISPETTO AD UN INDIVIDUO SANO DI AVERE UN FAMILIARE AFFETTO DALLA MP**

- **CASI ISOLATI (casi apparentemente sporadici ma con trasmissione autosomica recessiva della malattia)**

SCOPE OF GENETIC RESEARCH



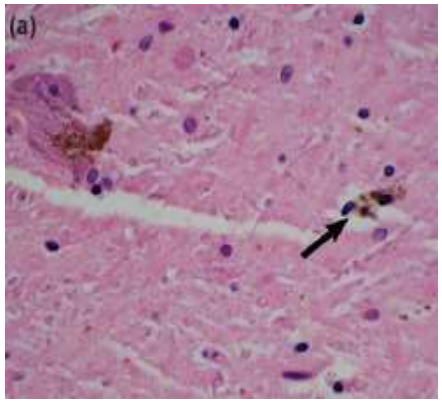
(Khoury, 1993)

STUDI DI EPIDEMIOLOGIA GENETICA

A. Trasmissione della patologia secondo le leggi mendeliane
   Studi sui casi familiari con trasmissione della malattia in maniera autosomica dominante o recessiva
   (studi di linkage)

B. Suscettibilità genetica all'insorgenza della malattia.
   Individuazione di polimorfismi associati all'insorgenza della malattia
   (studi di associazione allelica)

I LOCI E I GENI NELLA MALATTIA DI PARKINSON



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

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

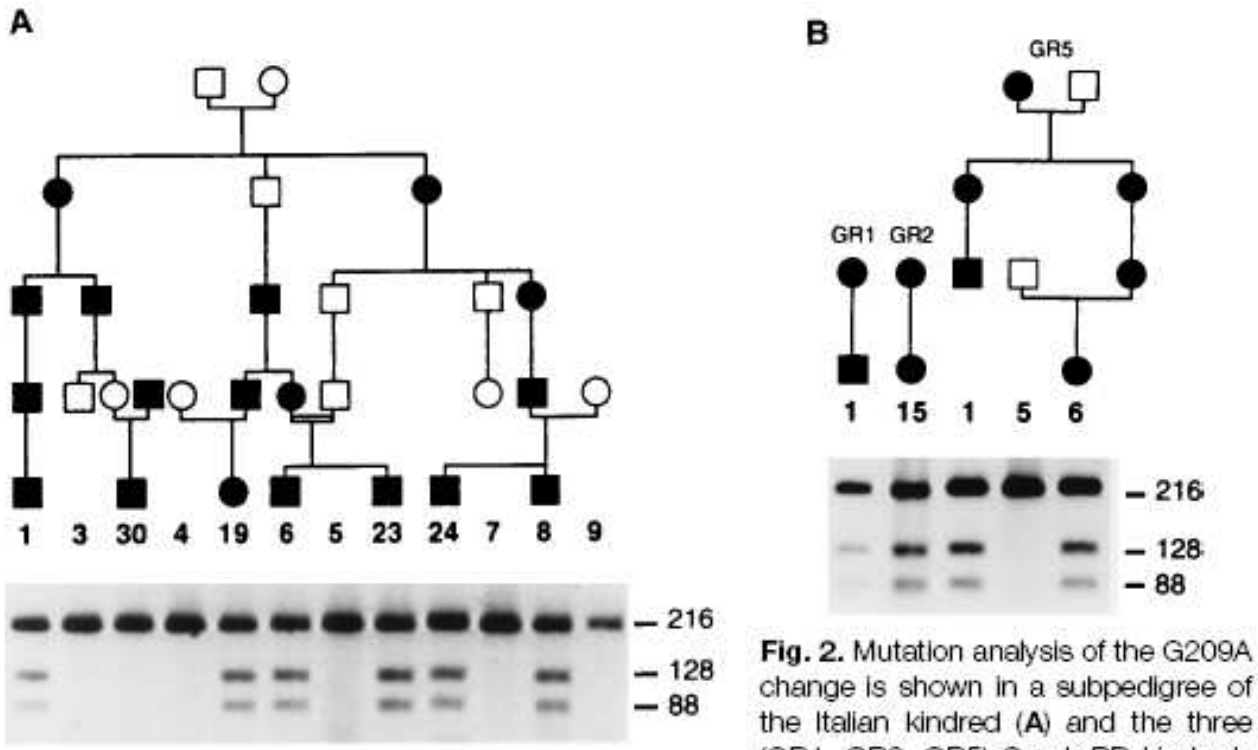


Fig. 2. Mutation analysis of the G209A change is shown in a subpedigree of the Italian kindred (**A**) and the three (GR1, GR2, GR5) Greek PD kindreds (**B**). Filled symbols represent affected individuals. Numerical identifiers denote the individuals immediately above. Tsp45 I digestion of PCR products (*5*) is shown at the bottom of the figure, and fragment sizes are indicated on the right in base pairs.

Genes and Loci for PD (1)

	Locus	Gene	Lewy-Bodies	Transm.
PARK-1	4q21-23	a-synuclein	Yes	Dominant
PARK-2	6q25q-27	parkin	No	Recessive
PARK-3	2p13	?	Yes	Dominant
PARK-4	4p15	a-synuclein	Yes	Dominant
PARK-5	4p14	UCH-L1	?	Dominant
PARK-6	1p35-36	?	?	Recessive
PARK-7	1p36	DJ-1	?	Recessive
PARK-8	12p11-q13	?	No	Dominant
PARK-9	1p36	?	?	Recessive
PARK-10	1p32	?	?	Non Mendelian
PARK-11	2q36-q37	?	?	Non Mendelian
Pending	2q22-q23	NR4A2 (NURR1)	?	Dominant

Genes and Loci for PD (2)

Locus	Gene	Onset	Lewy-Bodies	Course
PARK-1	a-synuclein	40ties	Yes	aggressive
PARK-2	parkin	30ties	No	slow
PARK-3	chr.2p13	50ties	Yes	more typical
PARK-4	a-synuclein	50ties	Yes	aggressive
PARK-5	UCH-L1	30ties	?	aggressive
PARK-6	chr.1p	40ties	?	slow
PARK-7	DJ-1	40ties	?	slow
PARK-8	LRRK2	50ties	No	more typical
PARK 9	chr-1p	20ties	?	aggressive
PARK10	chr.1p	60ties	?	more typical
PARK11	chr.-2q	60ties	?	more typical
Pending	NR4A2(NURR1A)	50ties	?	more typical

Table 1. Current catalogue of genes and loci for PD

Locus	Position	Gene	Inheritance pattern	Pathology	Clinical features
PARK1	4q21–q23	***SNCA (α-synuclein)***	dominant, high penetrance	LB tau pathology	early onset, aggressive course, dementia, severe autonomic disturbances in some cases
PARK3	2p13	unknown	dominant, incomplete penetrance	LB β-amyloid tau pathology	late onset, classical PD, dementia in some cases
PARK5	4p14	***UCHL1***	likely dominant	unknown	classical PD
PARK8	12p11–q13	unknown	dominant, incomplete penetrance	LB negative LB tau pathology	classical PD, dementia and amyotrophy in some cases
Pending	2q22–q23	***NR4A2 (NURR1)***	likely dominant	unknown	classical PD
PARK2	6q25–q27	***parkin***	recessive	mostly LB negative LB (1 case) tau pathology	early onset slow progression good, prolonged response to l-dopa, dystonia at onset, sleep benefit
PARK6	1p36–p35	***PINK1***	recessive	unknown	early onset, slow progression
PARK7	1p36	***DJ-1***	recessive	unknown	early onset, slow progression
PARK9	1p36	unknown	recessive	unknown	juvenile onset, multisystemic involvement, l-dopa response
PARK10	1p32	unknown	non-Mendelian	unknown	classical PD (Icelandic population)
PARK11	2q36–q37	unknown	non-Mendelian	unknown	classical PD (sib pairs study)
Pending	Xq	unknown	non-Mendelian	unknown	classical PD (sib pairs study)

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Early onset parkinsonism and *parkin* gene mutations

The European Consortium for Genetic Susceptibility in Parkinson's Disease

Study sample

- **73 families** l-dopa responsive pure parkinsonism
  - possible recessive inheritance
  - 2 affected sibs, onset <45 in one

- **100 isolated PD cases** with onset <45

Italy	20
France	14
UK	12
Netherlands	10
Germany	9
Others	8

Methods

-**semiquantitative PCR assay**

-for exon rearrangements (all 173 index cases)

- sequencing of coding regions (exons 1-12)

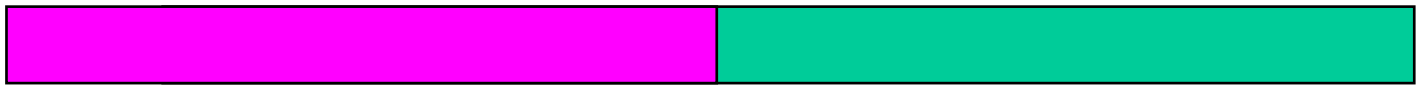
(103 of 145 index cases without 2 exon rearrangements)

Early onset parkinsonism and *parkin* gene mutations

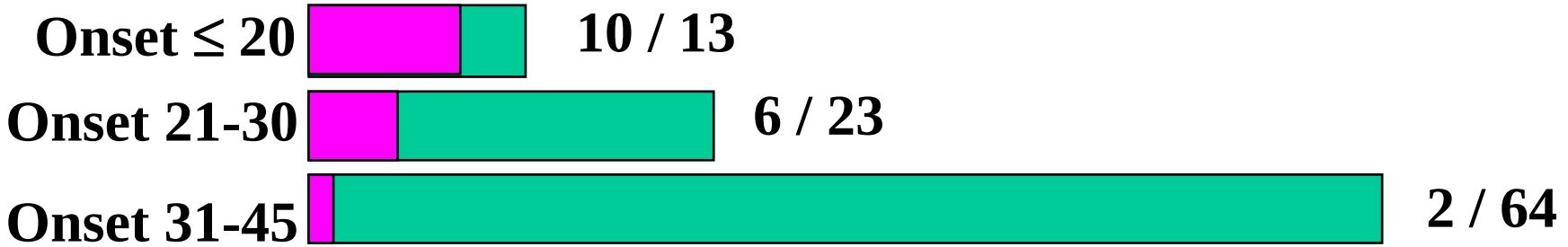
The European Consortium for Genetic Susceptibility in Parkinson's Disease

Molecular genetics results: mutation frequencies

families 49 % 36 / 73



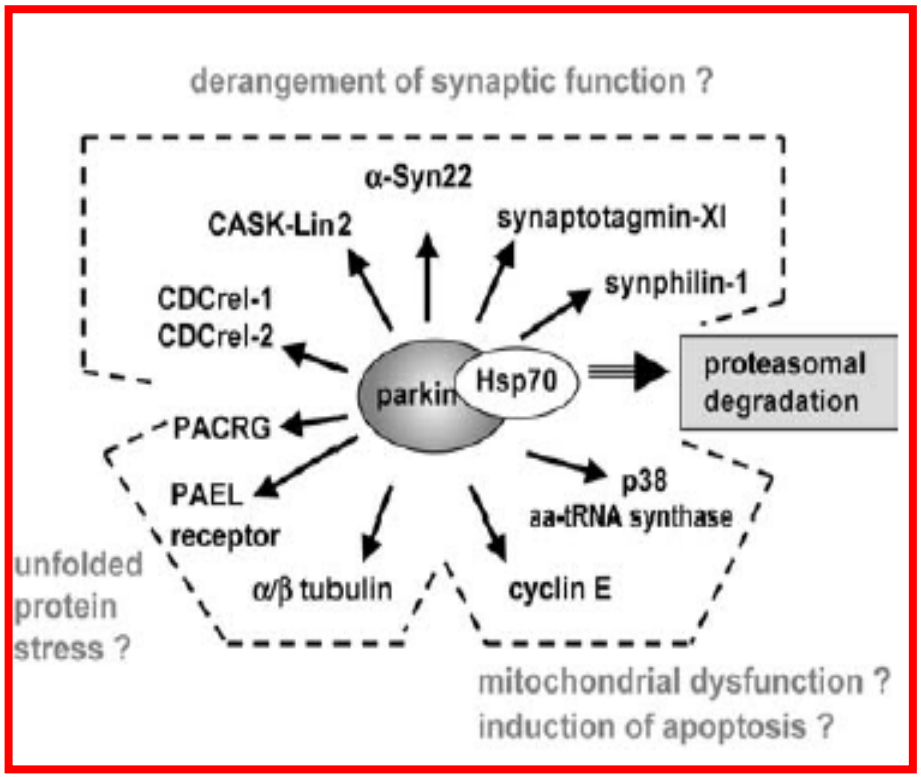
isolated cases: 18 % 18 / 100



Biomedicine and Diseases: Review

Unraveling the pathogenesis of Parkinson's disease – the contribution of monogenic forms

V. Bonifati[a,b,*], B. A. Oostra[a] and P. Heutink[c]



Malattia della parkina- Caratteristiche che orientano verso una possibile diagnosi (1) (2500 casi prevalenti in Italia stimatibili)

- Parkinsonismo a esordio giovanile (prima dei 40 anni)
- Altri germani affetti
- Casi sporadici di Parkinson con esordio molto precoce (prima dei 30 anni)
- Consanguineita' tra genitori
- Esordio con distonie all'arto inferiore
- Vivacita' dei riflessi osteo-tendinei
- Fluttuazione diurne della gravita' dei sintomi
- Sleep benefit

Malattia della parkina- Caratteristiche che orientano verso una possibile diagnosi (2)

- Ottima risposta alla L-Dopa
- Progressione molto lenta
- Presenza di fluttuazioni motorie indotte dalla L-Dopa
- Presenza di discinesie indotte dalla L-Dopa
- Assenza di gravi disturbi cognitivi
- Assenza di gravi disautonomie

Mutations in the *DJ-1* Gene Associated with Autosomal Recessive Early-Onset Parkinsonism

Vincenzo Bonifati,[1,2*] Patrizia Rizzu,[1] Marijke J. van Baren,[1] Onno Schaap,[1] Guido J. Breedveld,[1] Elmar Krieger,[3] Marieke C. J. Dekker,[1] Ferdinando Squitieri,[4] Pablo Ibanez,[5] Marijke Joosse,[1] Jeroen W. van Dongen,[1] Nicola Vanacore,[2,6] John C. van Swieten,[7] Alexis Brice,[5] Giuseppe Meco,[2] Cornelia M. van Duijn,[1] Ben A. Oostra,[1] Peter Heutink[1*]

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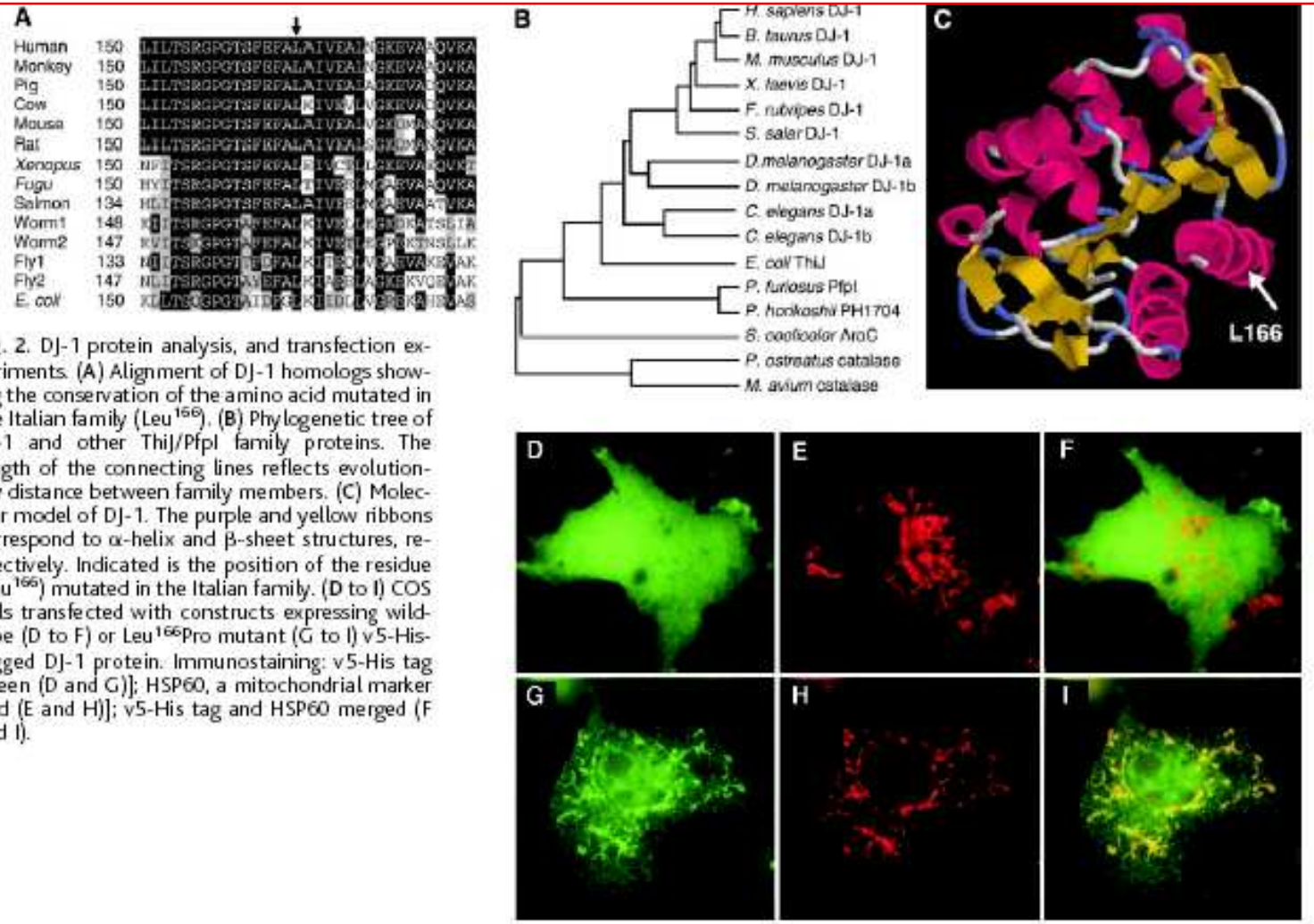
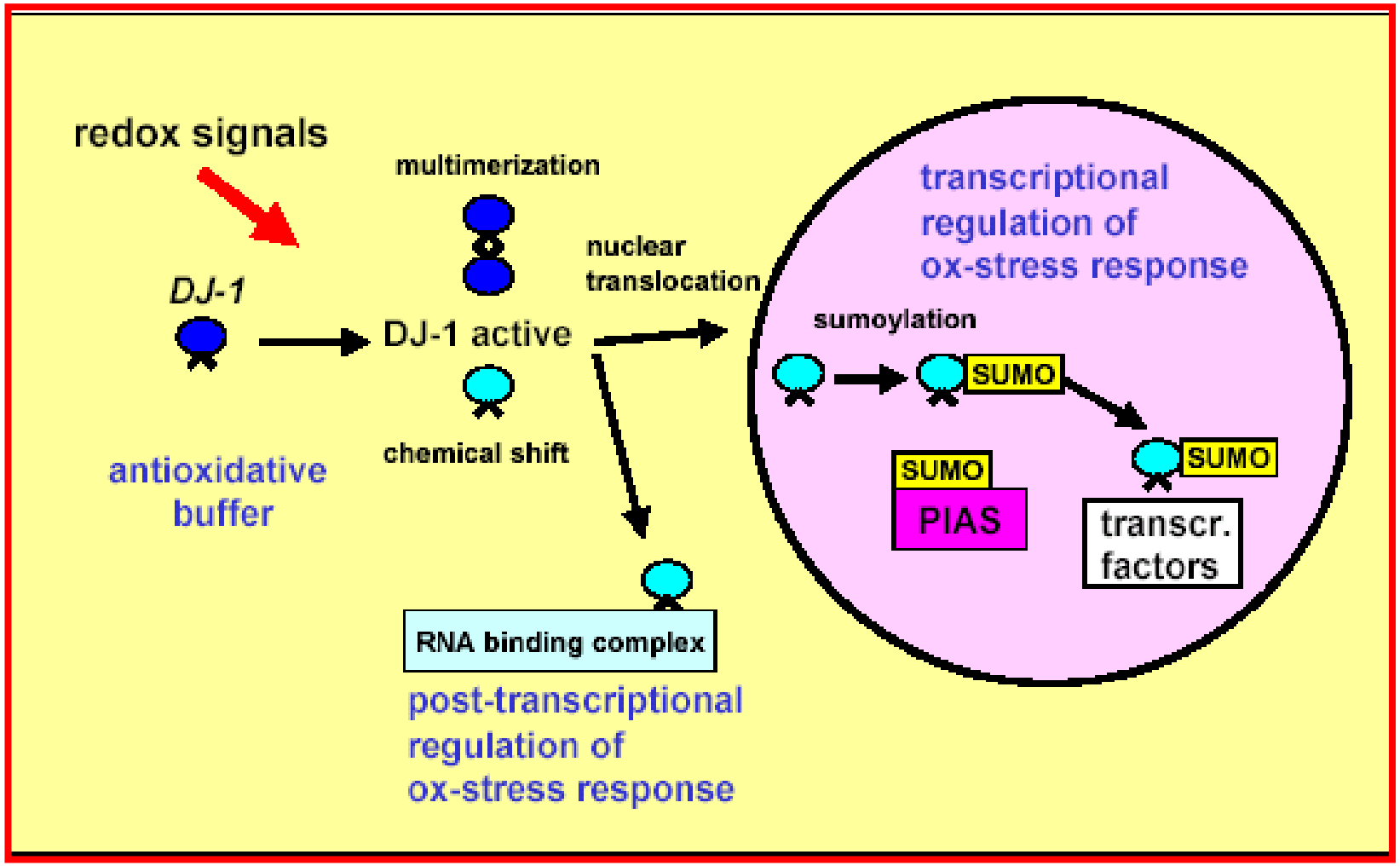


Fig. 2. DJ-1 protein analysis, and transfection experiments. (A) Alignment of DJ-1 homologs showing the conservation of the amino acid mutated in the Italian family (Leu^{166}). (B) Phylogenetic tree of DJ-1 and other ThiJ/PfpI family proteins. The length of the connecting lines reflects evolutionary distance between family members. (C) Molecular model of DJ-1. The purple and yellow ribbons correspond to α-helix and β-sheet structures, respectively. Indicated is the position of the residue (Leu^{166}) mutated in the Italian family. (D to I) COS cells transfected with constructs expressing wild-type (D to F) or Leu^{166}Pro mutant (G to I) v5-His-tagged DJ-1 protein. Immunostaining: v5-His tag [green (D and G)]; HSP60, a mitochondrial marker [red (E and H)]; v5-His tag and HSP60 merged (F and I).


redox signals
multimerization
nuclear
translocation
DJ-1
DJ-1 active
chemical shift
antioxidative
buffer
transcriptional
regulation of
ox-stress response
sumoylation
SUMO
SUMO
SUMO
PIAS
transcr.
factors
RNA binding complex
post-transcriptional
regulation of
ox-stress response

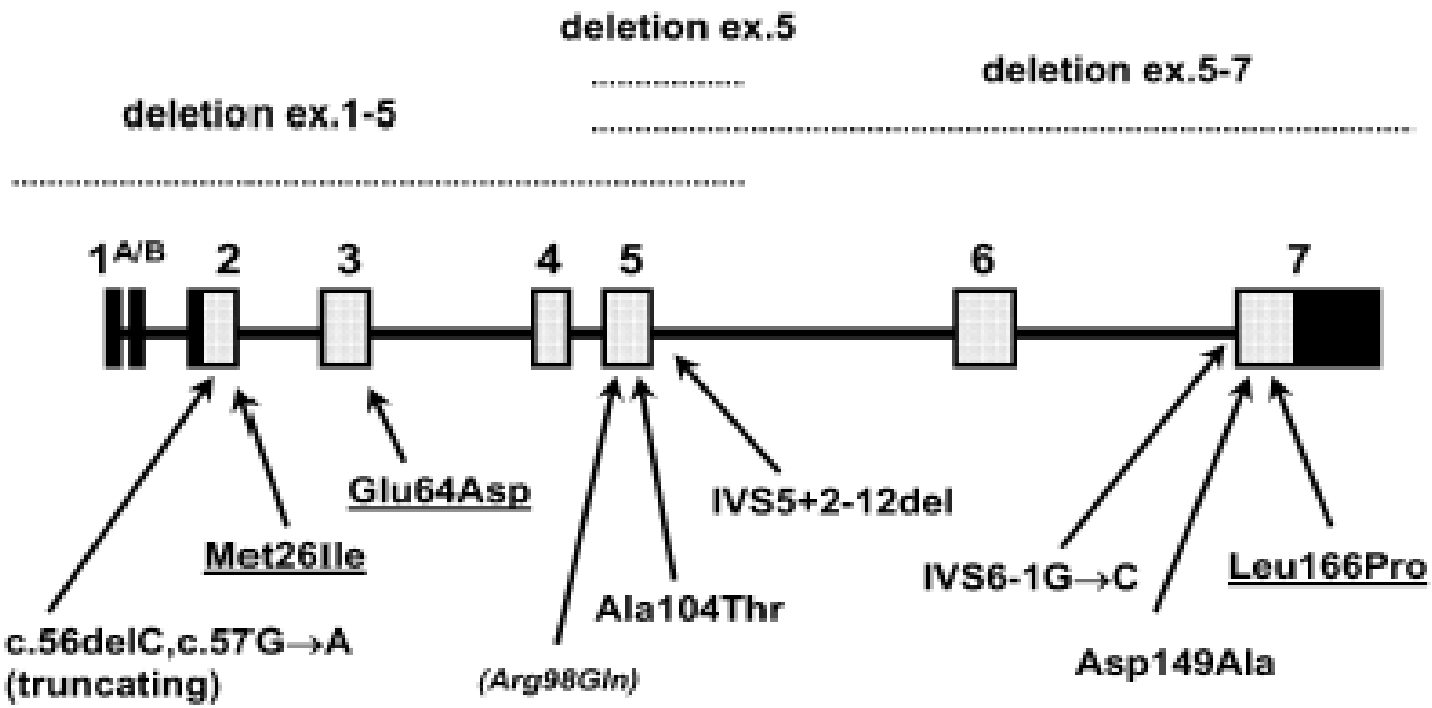


Fig. 1 Genomic structure of the *DJ-1* gene and mutations identified in PD. *Dark boxes* Noncoding exonic sequence; *light boxes* coding exonic sequence. Three missense mutations observed in homozygous form are underlined. The Arg98Gln change is a rare polymorphic variant observed in approx. 1.5% of control chromosomes in whites (K. Hedrich et al., submitted)

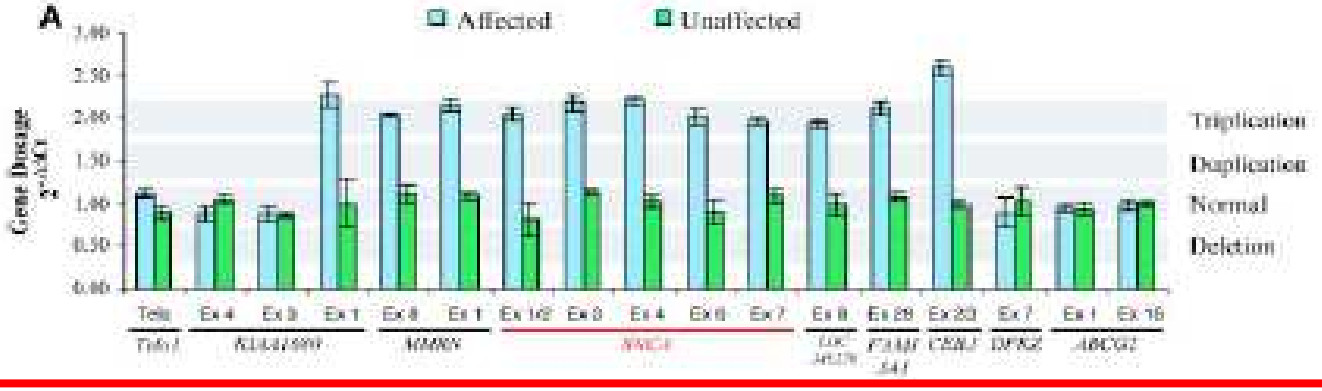
Bonifati 2005

α-Synuclein Locus Triplication Causes Parkinson's Disease

A. B. Singleton,[1]*† M. Farrer,[4]† J. Johnson,[1] A. Singleton,[2] S. Hague,[1] J. Kachergus,[4] M. Hulihan,[4] T. Peuralinna,[1] A. Dutra,[3] R. Nussbaum,[2] S. Lincoln,[4] A. Crawley,[2] M. Hanson,[1] D. Maraganore,[5] C. Adler,[6] M. R. Cookson,[1] M. Muenter,[6] M. Baptista,[1] D. Miller,[1] J. Blancato,[7] J. Hardy,[1] K. Gwinn-Hardy[2]

Mutations in the α-synuclein gene (*SNCA*) in the Contursi kindred (*1*) implicated this gene in Parkinson's disease (PD). Subsequently, α-synuclein was identified as the major component of Lewy bodies, the pathological hallmark of PD, and of glial cell cytoplasmic inclusions (*2*).

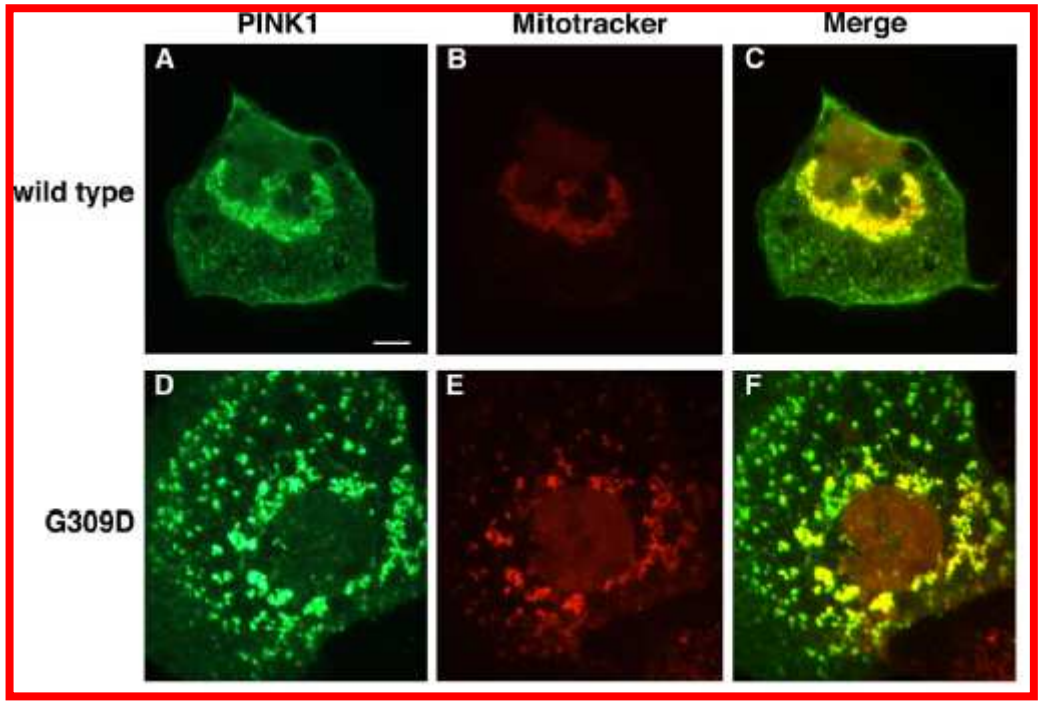
cM (*D4S2367–D4S1560*), with a multipoint LOD of 3.50 at *D4S2460*. The *SNCA* genotypes were inconsistent with previous data, leading to initial exclusion; re-evaluation of the original linkage revealed a sample swap. Resequencing of *SNCA* failed to reveal pathogenic mutations.

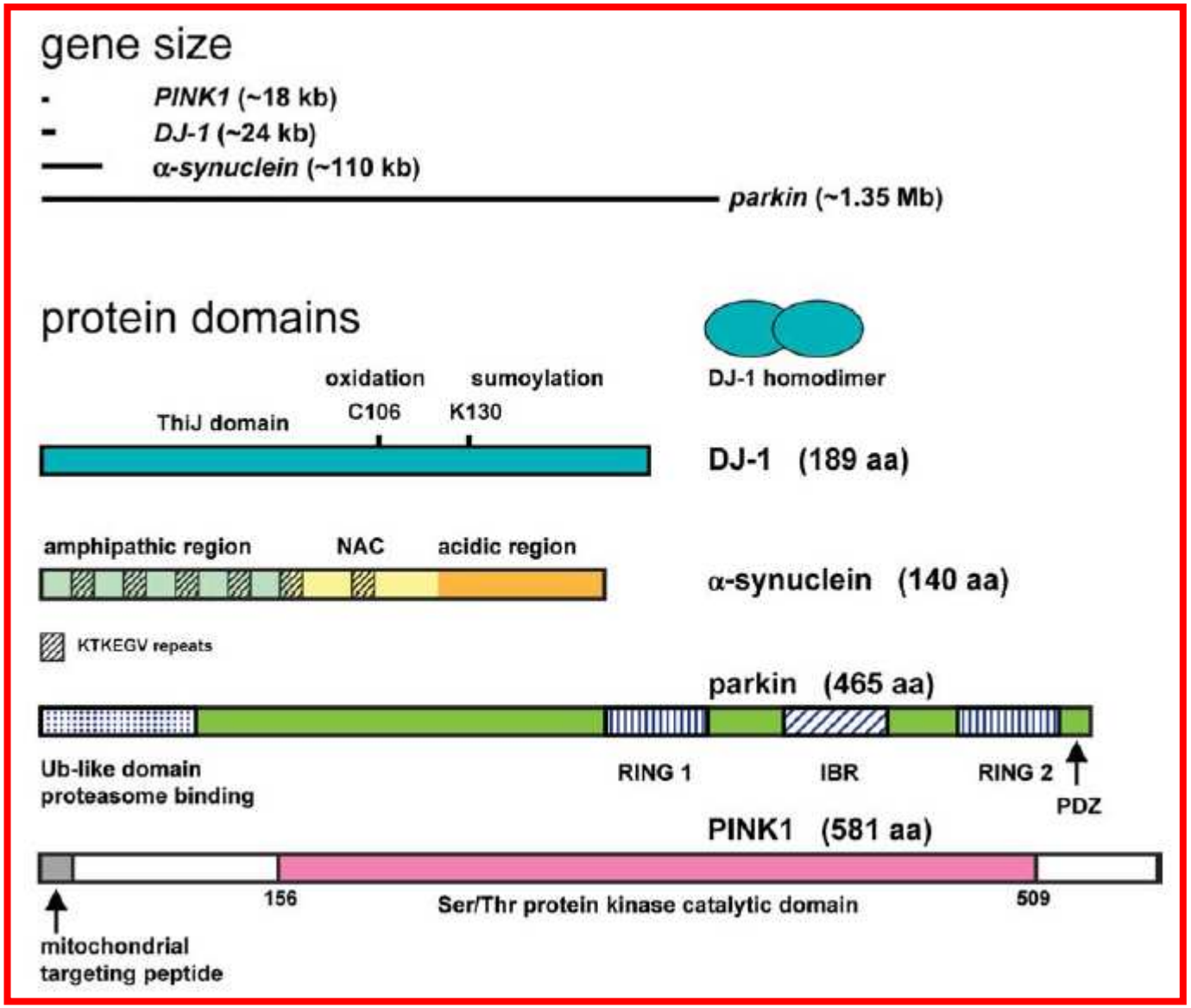


Sciencexpress Report

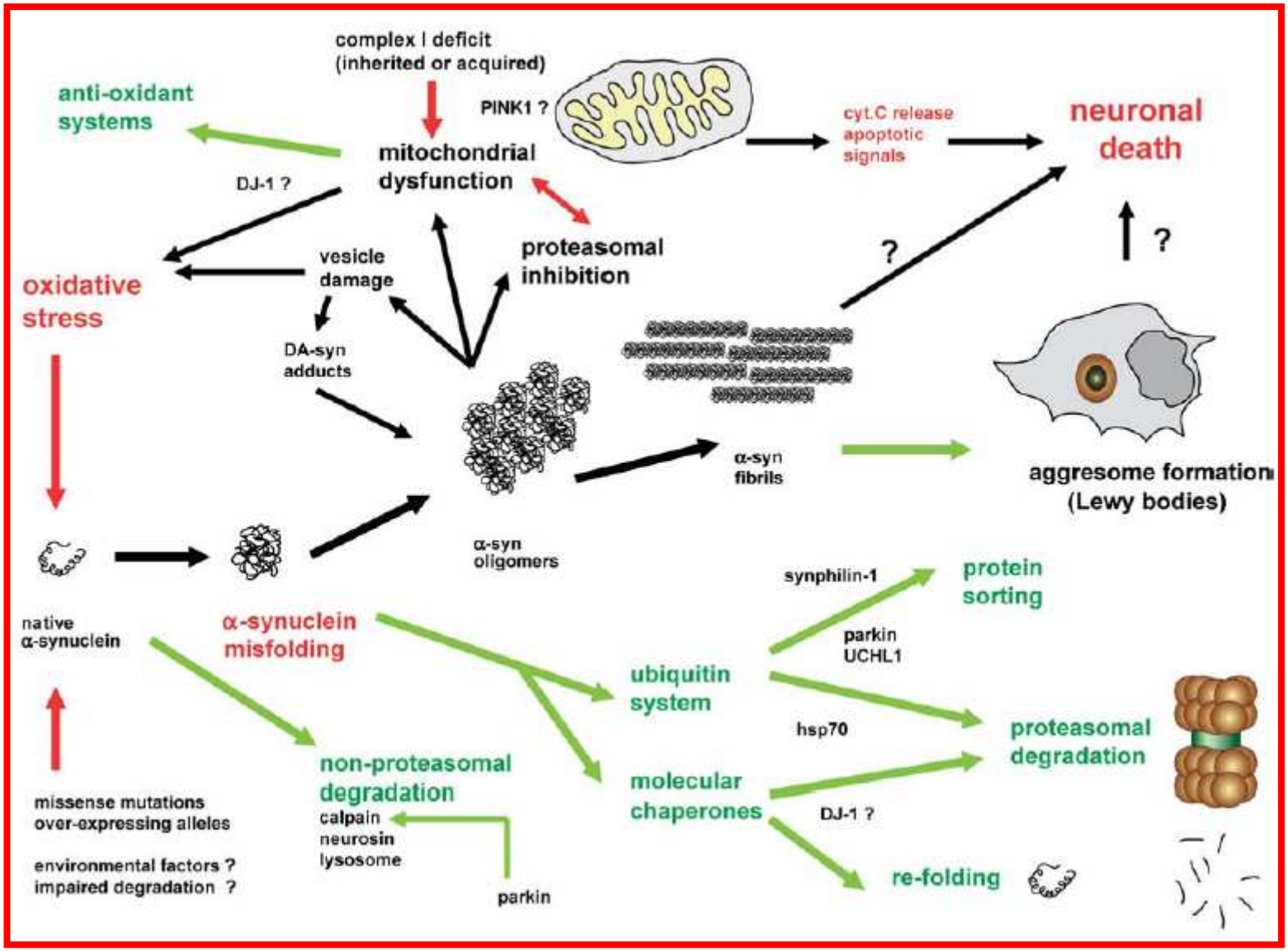
Hereditary Early-Onset Parkinson's Disease Caused by Mutations in *PINK1*

Enza Maria Valente,[1*‡] Patrick M. Abou-Sleiman,[2*] Viviana Caputo,[1,3†] Miratul M. K. Muqit,[2,4†] Kirsten Harvey,[5] Suzana Gispert,[6] Zeeshan Ali,[6] Domenico Del Turco,[7] Anna Rita Bentivoglio,[8] Daniel G Healy,[2] Alberto Albanese,[9] Robert Nussbaum,[10] Rafael González-Maldonado,[11] Thomas Deller,[7] Sergio Salvi,[1] Pietro Cortelli,[12] William P. Gilks,[2] David S. Latchman,[4,13] Robert J. Harvey,[5] Bruno Dallapiccola,[1,3] Georg Auburger,[14‡] Nicholas W. Wood[2‡]





Bonifati 2005



Bonifati 2005

A frequent *LRRK2* gene mutation associated with autosomal dominant Parkinson's disease

*Alessio Di Fonzo, Christan F Rohé, Joaquim Ferreira, Hsin F Chien, Laura Vacca, Fabrizio Stocchi, Leonor Guedes, Edito Fabrizio, Mario Manfredi, Nicola Vanacore, Stefano Goldwurm, Guido Breedveld, Cristina Sampaio, Giuseppe Meco, Egberto Barbosa, Ben A Oostra, Vincenzo Bonifati, and the Italian Parkinson Genetics Network**

Mutations in the *LRRK2* gene have been identified in families with autosomal dominant parkinsonism. **We amplified and sequenced the coding region of *LRRK2* from genomic DNA by PCR, and** identified a heterozygous mutation (Gly2019Ser) present in four of 61 (6·6%) unrelated families with Parkinson's disease and autosomal dominant inheritance. The families originated from Italy, Portugal, and Brazil, indicating the presence of the mutation in different populations. The associated phenotype was broad, including early and late disease onset. These findings confirm the association of *LRRK2* with neurodegeneration, and identify a common mutation associated with dominantly inherited Parkinson's disease.

ELECTRONIC LETTER

The G6055A (G2019S) mutation in *LRRK2* is frequent in both early and late onset Parkinson's disease and originates from a common ancestor

S Goldwurm*, A Di Fonzo*, E J Simons, C F Rohé, M Zini, M Canesi, S Tesei, A Zecchinelli, A Antonini, C Mariani, N Meucci, G Sacilotto, F Sironi, G Salani, J Ferreira, H F Chien, E Fabrizio, N Vanacore, A Dalla Libera, F Stocchi, C Diroma, P Lamberti, C Sampaio, G Meco, E Barbosa, A M Bertoli-Avella, G J Breedveld, B A Oostra, G Pezzoli, V Bonifati

J Med Genet 2005;**42**:e (http://www.jmedgenet.com/cgi/content/full/42/11/e65). doi: 10.1136/jmg.2005.035568

GENE LRKK2 - DARDARINA

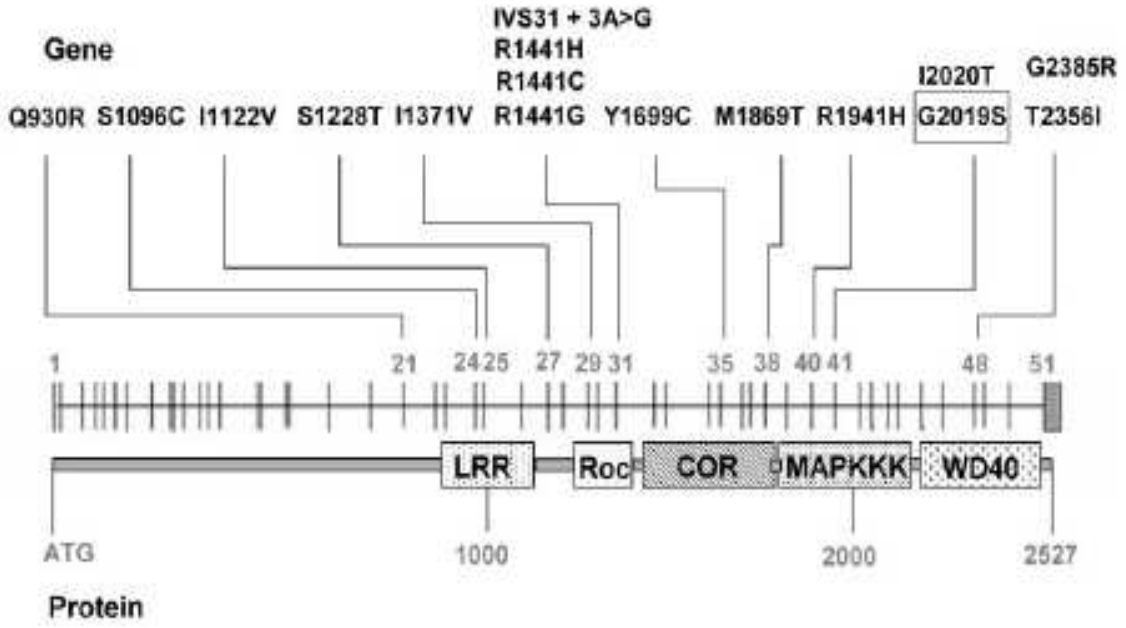


Fig. 1. Genomic and protein structures of *LRRK2*. The gene contains 51 exons. All the 16 putatively pathogenic *LRRK2* mutations considered as pathogenic are positioned along the gene. The most frequent LRRK2 G2019S mutation in exon 41 is boxed. Functional domains: LRR, leucine rich repeat; ROC, Ras of complex proteins; COR, C-terminal of Roc; MAPKKK, mitogen activated kinase kinase kinase; WD40, β-propeller.

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SCIENCE DIRECT
Neuroscience Letters xxx (2005) xxx–xxx
Neuroscience Letters
www.elsevier.com/locate/neulet

LRRK2 G2019S is a common mutation in Spanish patients with late-onset Parkinson's disease

Jon Infante[a,*], Eloy Rodríguez[a], Onofre Combarros[a], Ignacio Mateo[a], Ana Fontalba[b], Julio Pascual[a], Agustín Oterino[a], José María Polo[a], Carlos Leno[a], José Berciano[a]

[a] *Service of Neurology, University Hospital "Marqués de Valdecilla", University of Cantabria, 39008 Santander, Spain*
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Received 30 June 2005; received in revised form 16 August 2005; accepted 29 October 2005

Abstract

Mutations in the leucine-rich repat kinase 2 (*LRRK2*) gene have been shown to cause both autosomal dominant and sporadic Parkinson's disease (PD). The common G2019S mutation shows wide geographical distribution while R1441G has been only reported in Northern Spain. The overall frequency of these mutations remains to be established. To determine the prevalence of G2019S and R1441G mutations in our population of Cantabria (Northern Spain), we recruited 105 consecutive PD patients and 310 controls and conducted genetic analysis of these mutations. G2019S was detected in eight late-onset patients (7.6%). Five of them had no relevant family history. R1441G was not detected in any of our study subjects. The prevalence of G2019S mutation in unselected late-onset PD patients might be higher than previously reported: 3/16 (18.7%) of familial PD and 5/82 (6.1%) of sporadic PD.

Table 2
Prevalence of G2019S mutation in various studied populations

Author	Simple size	Type of PD	Race	Country	Prevalence (%)
Gilks et al. [5]	482	Sporadic	White	UK	1.6 (two familial, six sporadic)
Nichols et al. [10]	767	Familial	White 94%, Hispanic 5%	USA	5
Di Fonzo et al. [3]	61	Familial AD	Not reported	Italy, Brazil, Portugal	6.6
Paisán-Ruiz et al. [12]	121	EOPD 84%, familial 42%	White 91%	Canada	1.6 (two familial AD)
Aasly et al. [1]	435	Sporadic 85%, familial 15%	Not reported	Norway	2 (six familial AD, three sporadic)
Kachergus et al. [7]	248	Familial AD	Not reported	USA, Europe, Asia	2.8
	806	Idiopathic PD	Not reported	Norway, Ireland, Poland	0.7 (three familial AD, three sporadic)
Tan et al. [13]	675	Sporadic 61%, EOPD 30%, familial 8.6%	Chinese 84%	Singapore	0
Farrer et al. [4]	786	Sporadic 70%, familial 30%	White	USA	0.5 (All familial)
Zabetian et al. [14]	371	Sporadic 89%, familial 11%	White	USA	0.8 (one familial, two sporadic)
Deng et al. [2]	326	Sporadic 54%, familial 46%	Not reported	USA	1.2 (three familial, one sporadic)
Lesage et al. [8]	200	Familial AD	Not reported	North-Africa, Europe	41 (North-Africa), 2.8 (Europe)
Present study	105	Sporadic 78%, EOPD 6.6%, familial 15%	White	Spain	7.6 (three familial, five sporadic)

EOPD: early-onset Parkinson's disease; familial: 1 or more first degree affected relatives.

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(Lesage 2006)

Table 1. Frequency of the G2019S Mutation in North African Arabs with Familial and Sporadic Parkinson's Disease and in Ethnically Matched Controls.

Type of Case and Study	Patients	Controls	P Value*
	no. with mutation/total no. (%)		
Familial			
Previous study†	7/17 (41)	0/82	<0.001
Present study	3/10 (30)	2/69 (3)	0.01
Combined studies	10/27 (37)	2/151 (1)‡	<0.001
Sporadic			
Present study	20/49 (41)	2/151 (1)‡	<0.001

* P values were calculated with the use of Fisher's exact test.
† Data are from Lesage et al.[2]
‡ Controls are from the present study (69) and the previous study (82).

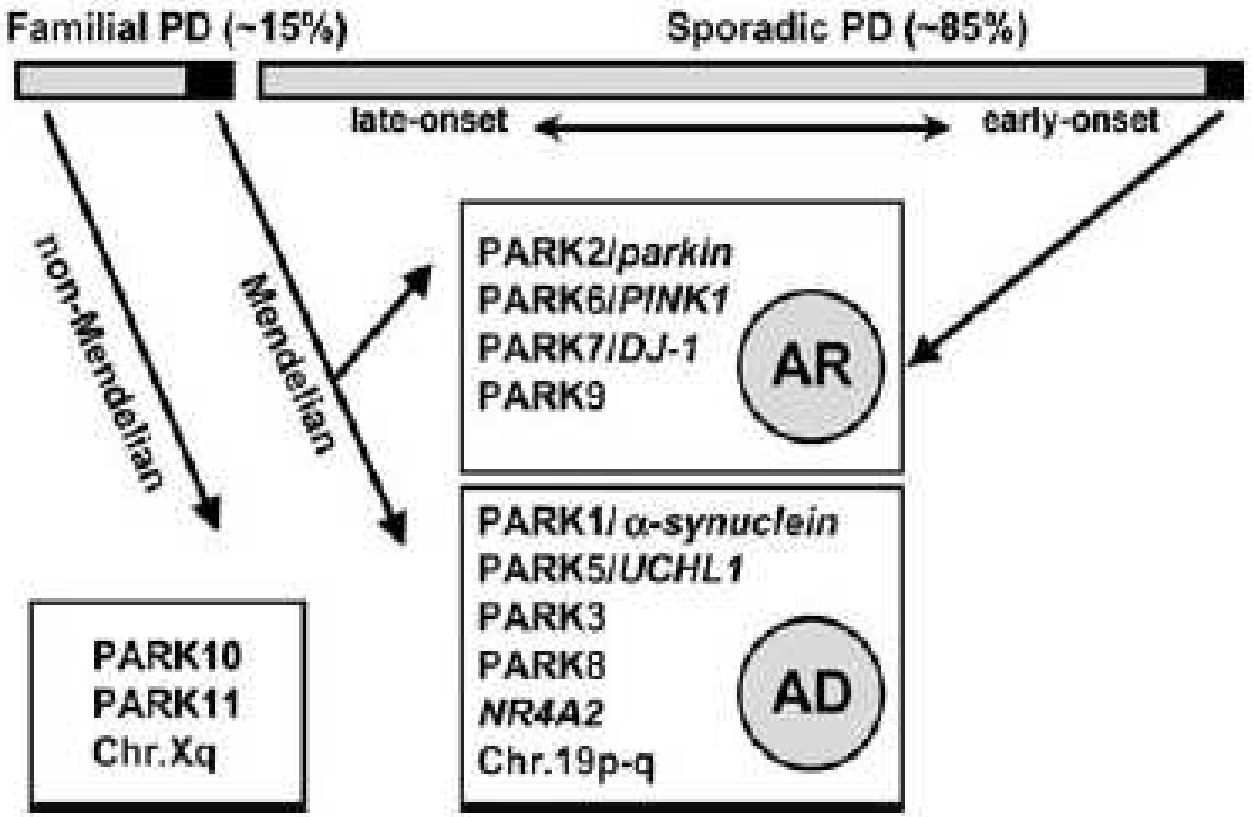


Figure 1. Inheritance patterns and genetic loci for PD. Linkage analysis and positional cloning have recently led to the identification of genes and loci for Mendelian and non-Mendelian forms of PD. AR, autosomal recessive; AD, autosomal dominant.

Bonifati 2005

PREVALENZA DLLE MUTAZIONI PARKINSONIANE

GENI	PD SPORADICI	PD FAMILIARI
Alfa-synucleina	_	qualche unità
DJ-1	1-2%	1%
Parkin	18% (< 50yrs)	49% (<50yrs)
PINK-1	1-2%	1%
LRRK2	3-7%	1-2%

SUSCETTIBILITA' GENETICA NELLA MALATTIA DI PARKINSON

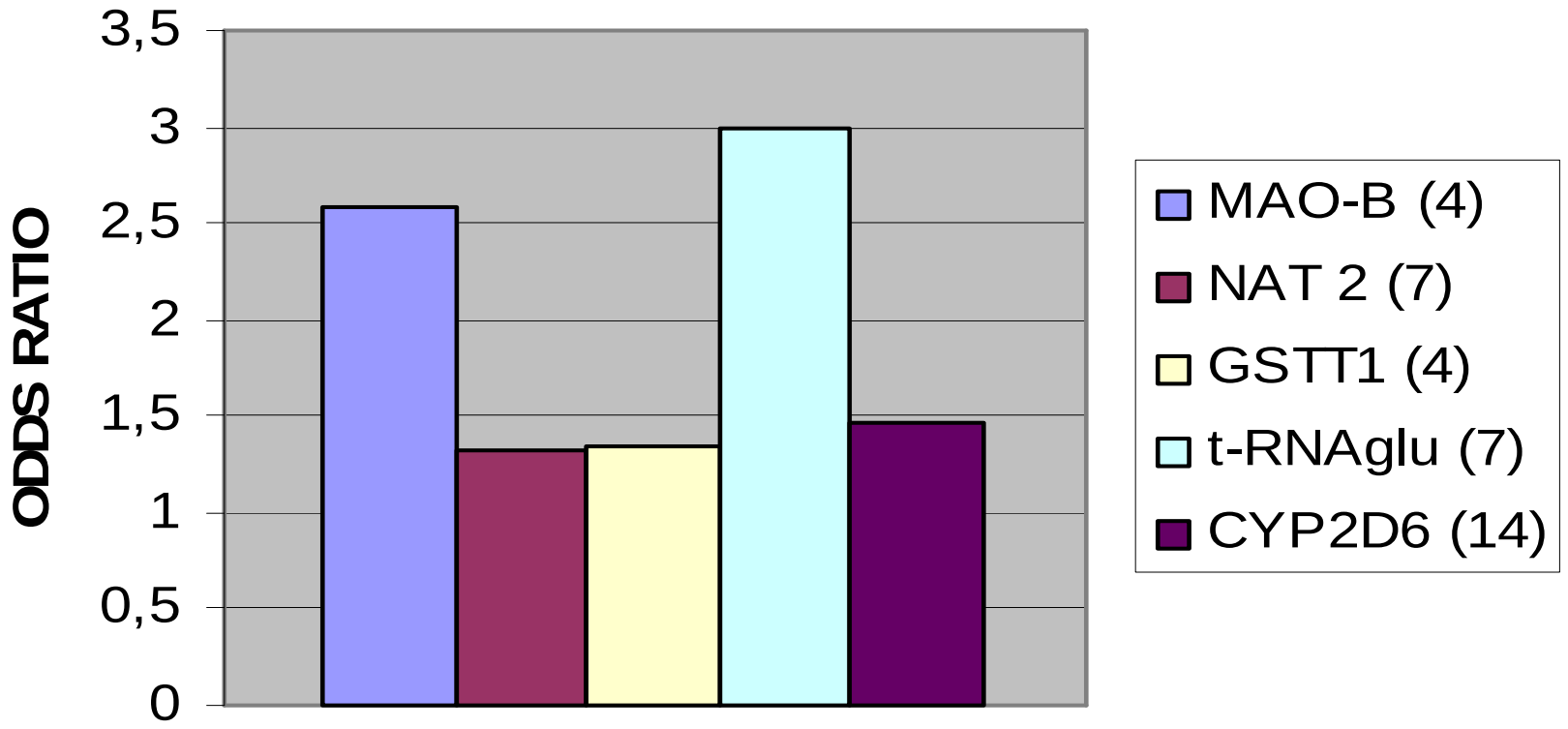
STUDI DI ASSOCIAZIONE ALLELICA NELLA MALATTIA DI PARKINSON

GENI	MP vs Controlli
Citocromo P450 2D6	lenti metaboliz. vs veloci
Glutatione transferasi	GSTT1
	delezioni vs non delezioni
N.-acetiltransferasi 2	lenti acetilatori vs veloci
MAO-B	GTn dinucleotide repeat polymorphism
	allele > 188 vs > 188
tRNA ^{glu}	mutaz.puntiforme A4336G

STUDI DI ASSOCIAZIONE ALLELICA

(STUDI DI META-ANALISI)

(Tan EK 2000, McCann SJ 1997)



Am. J. Hum. Genet. 72:804–811, 2003

Mitochondrial Polymorphisms Significantly Reduce the Risk of Parkinson Disease

Joelle M. van der Walt,[1,2] Kristin K. Nicodemus,[1,2] Eden R. Martin,[1,2] William K. Scott,[1,2] Martha A. Nance,[3] Ray L. Watts,[4] Jean P. Hubble,[5] Jonathan L. Haines,[6] William C. Koller,[7] Kelly Lyons,[7] Rajesh Pahwa,[8] Matthew B. Stern,[9] Amy Colcher,[9] Bradley C. Hiner,[10] Joseph Jankovic,[11] William G. Ondo,[11] Fred H. Allen Jr.,[12] Christopher G. Goetz,[13] Gary W. Small,[14,15] Frank Mastaglia,[16] Jeffrey M. Stajich,[1,2] Adam C. McLaurin,[1,2] Lefkos T. Middleton,[17] Burton L. Scott,[3] Donald E. Schmechel,[1] Margaret A. Pericak-Vance,[1,2] and Jeffery M. Vance[1,2]

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DOPAMINE D_2 RECEPTOR GENE POLYMORPHISM AND THE RISK OF LEVODOPA INDUCED DYSKINESIAS IN PD (Neurology 1999;53:1425-430)

The intronic short tandem (STR) polymorphism of the DRD2 gene

	136 PD	224 control subjects	
Allele 15	172/272 (63.2%)	249/448 (55.6%)	p = 0.04

Update TRENDS in Genetics Vol.xx No.xx Monthxxxx

Letters Response

Response to Manly: Statistical stringency in tests of genetic association – implications for sample size and study design

Marcus R. Munafò[1], E. Paul Wileyto[2] and Jonathan Flint[3]

Table 1. Total study sample size required to achieve 80% power[a]

True effect size[b] (odds ratio)	Critical *P*-value[c]		
	0.05	0.001	0.0001
1.1	14 812	32 225	42 265
1.2	4006	8718	11 434
1.3	1919	4176	5477
1.4	1158	2522	3309
1.5	793	1728	2267

Negli studi di associazione allelica è molto elevata la probabilità di commettere un errore statistico di I tipo (falso positivo).

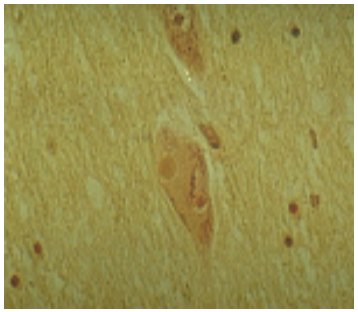
Per tali ragioni vengono oggi richiesti studi con elevata numerosità e con evidenze scientifiche con un p di almeno 0.001

Table 2 | **Approximate sample sizes needed to detect a significantly increased allelic odds ratio***

Disease allele frequency	Marker allele frequency	Allelic odds ratio of disease gene					
		3.0		2.0		1.3	
		No. cases (= no. controls)	No. cases: no. controls (= 1:4)	No. cases (= no. controls)	No. cases: no. controls (= 1:4)	No. cases (= no. controls)	No. cases: no. controls (= 1:4)
0.05	0.05	360	210:840	1110	650:2600	9500	5600:22400
	0.1	600	350:1400	2000	1200:4800	19000	11500:46000
	0.2	1170	700:2800	4150	2500:10000	40000	25000:100000
	0.3	1900	1200:4800	6800	4300:13200	70000	43000:172000
	0.5	4200	2700:10800	15000	9500:38000	160000	100000:400000
0.2	0.05	710	420:1680	1900	1090:4360	14000	8500:34000
	0.1	350	200:800	900	500:2000	6600	4400:13600
	0.2	150	85:340	360	220:880	2900	1750:7000
	0.3	210	130:520	530	360:1440	4800	3000:12000
	0.5	430	270:1080	1250	800:3200	11000	6950:27800
0.5	0.05	3150	1870:7480	6800	4000:16000	40000	25000:100000
	0.1	1500	900:3600	3200	2000:8000	19000	12000:48000
	0.2	640	390:1560	1350	850:3400	8500	5300:21200
	0.3	360	220:880	800	500:2000	5000	3100:12400
	0.5	140	90:360	320	200:800	2100	1300:5200

*Using diallelic markers with varying allele frequency and allowing linkage disequilibrium between marker and disease allele down to $D' = 0.7$, odds ratio (power ≈ 80%; $\alpha = 0.001$).

PROSPETTIVE



Am. J. Hum. Genet. 70:1089–1095, 2002

PARK3 Influences Age at Onset in Parkinson Disease: A Genome Scan in the *Gene*PD Study

Anita L. DeStefano,[1,2] Mark F. Lew,[4] Lawrence I. Golbe,[5] Margery H. Mark,[5] Alice M. Lazzarini,[5] Mark Guttman,[7] Erwin Montgomery,[6] Cheryl H. Waters,[4] Carlos Singer,[8] Ray L. Watts,[9] Lillian J. Currie,[10] G. Frederick Wooten,[10] Nancy E. Maher,[1] Jemma B. Wilk,[1] Kristin M. Sullivan,[1] Karen M. Slater,[1] Marie H. Saint-Hilaire,[1] Robert G. Feldman,[1] Oksana Suchowersky,[12] Anne-Louise Lafontaine,[12] Nancy Labelle,[12] John H. Growdon,[3] Peter Vieregge,[13] Peter P. Pramstaller,[14] Christine Klein,[13] Jean P. Hubble,[11] Carson R. Reider,[11] Mark Stacy,[15] Marcy E. MacDonald,[3] James F. Gusella,[3] and Richard H. Myers[1]

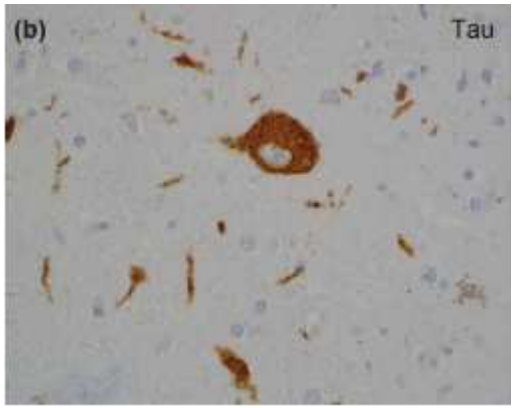
LRRK2 gene in Parkinson disease

Mutation analysis and case control association study

C. Paisán-Ruíz, PhD; A.E. Lang, MD; T. Kawarai, MD; C. Sato, BSc; S. Salehi-Rad, BSc; G.K. Fisman, MD; T. Al-Khairallah, MD; P. St George-Hyslop, MD; A. Singleton, PhD; and E. Rogaeva, PhD

NEUROLOGY 2005;65:696–700

Intriguingly, among at-risk members of the PD2 family we detected the G2019S *LRRK2* mutation in Case 5019 (V-4), who also has a heterozygous mutation in *PARKIN* resulting in a loss of function by truncation of the protein at codon 81. This *PARKIN* mutation is known to cause PD if inherited in a homozygous state.[22] *PARKIN* gene is typically responsible for a recessive early onset form of the disease; however, heterozygous mutations are being considered as a risk factor for late-onset PD.[23] In addition to the *LRRK2* and *PARKIN* mutations the same individual also inherited a heterozygous N370S mutation in the GBA gene, which has been suggested as a PD risk factor.[15-17] To our knowledge this is the first report of a triple mutant individual with pathologic aberrations in three different genes implicated in PD. Surprisingly the genetic makeup in this patient did not lead to early onset of PD (Case 5019 does not have any signs of PD at age 52).



FEBS 25011

FEBS Letters 500 (2001) 105–108

Pesticides directly accelerate the rate of α-synuclein fibril formation: a possible factor in Parkinson's disease

Vladimir N. Uversky, Jie Li, Anthony L. Fink*

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Received 23 May 2001; revised 7 June 2001; accepted 7 June 2001

First published online 19 June 2001

Edited by Jesus Avila

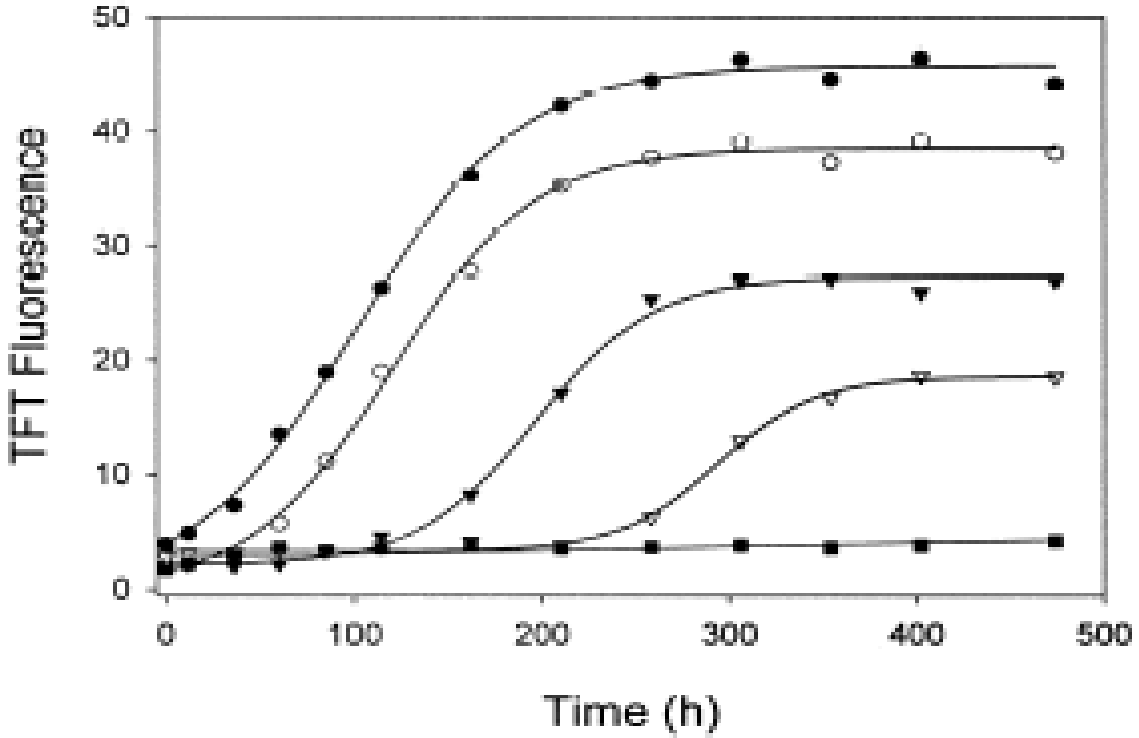

Fig. 1. Kinetics of α-synuclein fibril formation in the presence of pesticides. Solutions of α-synuclein (35 μM) were incubated with stirring at 37°C, in 10 mM phosphate buffer, pH 7.5, in the presence of the indicated pesticides (100 μM) as described in the text. Fibril formation was monitored by the increase in TFT fluorescence. Key: control, ■; DDC, ●; dieldrin, ○; paraquat, ▼; rotenone, ▽. The lag times (h) and rate constants for fibril growth (elongation) (h^{-1}) were as follows: DDC (9.9, 0.023), dieldrin (42.5, 0.026), rotenone (137.2, 0.035), and paraquat (241.2, 0.038).

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Neurobiology of Disease

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Neurobiology of Disease xx (2006) xxx – xxx

Intersecting pathways to neurodegeneration in Parkinson's disease: Effects of the pesticide rotenone on DJ-1, α-synuclein, and the ubiquitin–proteasome system

Ranjita Betarbet,[a,*] Rosa M. Canet-Aviles,[b] Todd B. Sherer,[a] Pier G. Mastroberardino,[a,f] Chris McLendon,[b] Jin-Ho Kim,[a] Serena Lund,[a] Hye-Mee Na,[a,f] Georgia Taylor,[a] Neil F. Bence,[c] Ron Kopito,[c] Byoung Boo Seo,[d] Takao Yagi,[d] Akemi Yagi,[d] Gary Klinefelter,[e] Mark R. Cookson,[b] and J. Timothy Greenamyre [a,f]

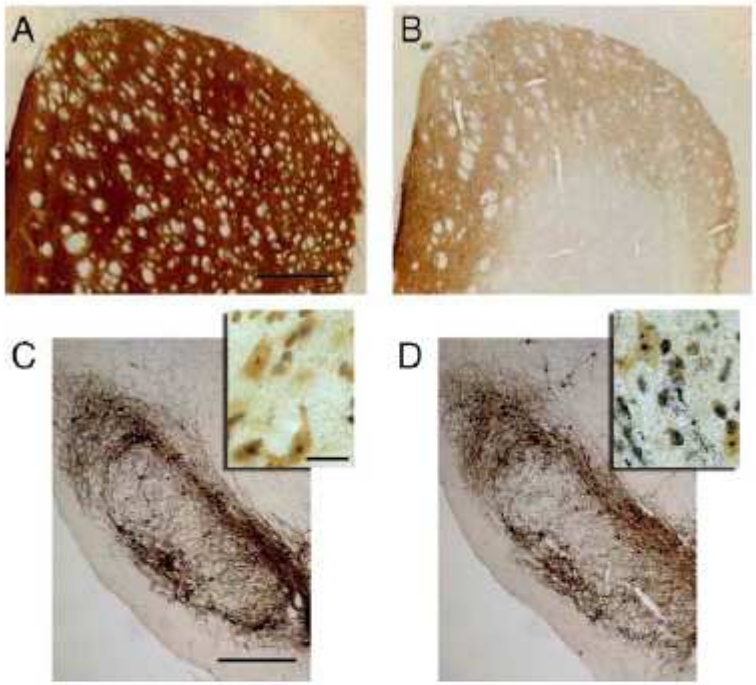
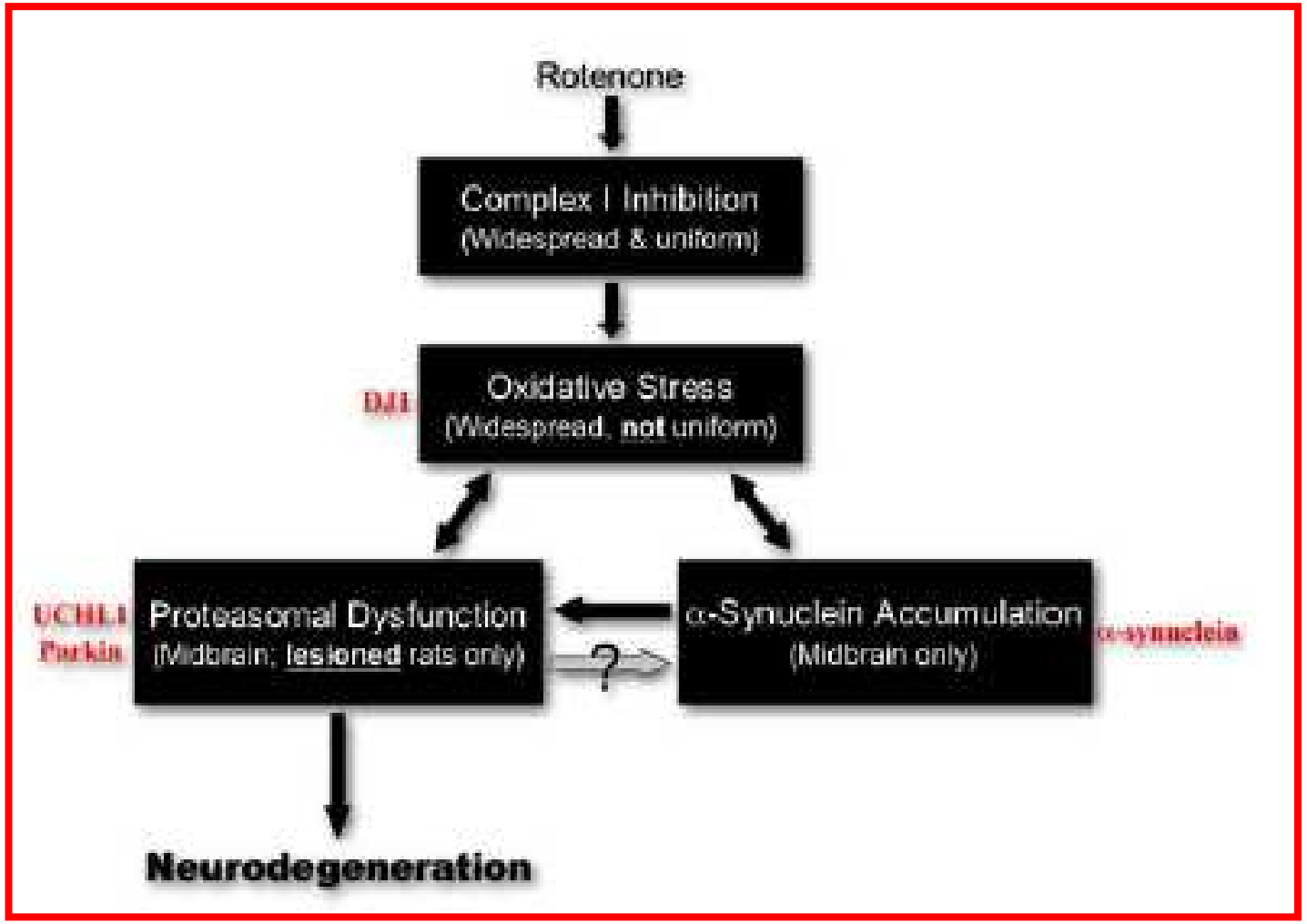


Fig. 1. Systemic rotenone infusion resulted in nigrostriatal dopaminergic degeneration. Coronal sections through striatum and substantia nigra (SN) from control (A and C) and rotenone-infused rats (3.0 mg/kg/day; B and D) were immunostained for TH. Sections through SN were also processed for silver staining for neurodegeneration (insets in C and D). Rotenone infusion resulted in striatal dopaminergic denervation as evident from loss of TH-immunoreactivity (TH-ir) in the striatum (B) compared to control striatum (A). TH-ir appeared to be relatively normal in the SN from rotenone-infused rats (C and D). However, silver staining showed degenerating processes with silver deposits in SN suggesting retrograde degeneration of the nigrostriatal dopaminergic pathway. Scale bar for panels A, B, C, and D is 500 μm and for the inset is 20 μm.


Rotenone
Complex I Inhibition
(Widespread & uniform)
DJ1
Oxidative Stress
(Widespread, not uniform)
UCHL1
Parkin
Proteasomal Dysfunction
(Midbrain; lesioned rats only)
?
α-Synuclein Accumulation
(Midbrain only)
α-synuclein
Neurodegeneration

REVIEW

Review

Epidemiological methods for studying genes and environmental factors in complex diseases

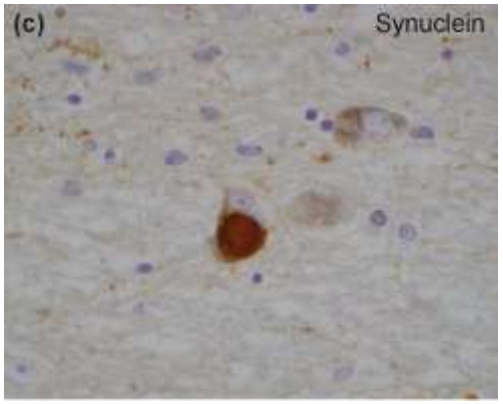
David Clayton, Paul M McKelgue

Environmental exposure	Positive genotype		Negative genotype	
	Cases	Controls	Cases	Controls
Yes	*a*	*b*	*e*	*f*
No	*c*	*d*	*g*	*h*
Odds ratio	$\frac{ad}{bc}$		$\frac{eh}{fg}$	

Table 2: **Odds ratios for association of disease with environmental exposure, by genotype**

OR int = OR susc/OR non susc

STUDI FARMACOLOGICI IN FASE PRECLINICA



INIBITORE DELL'AGGREGAZIONE DELL'ALFA-SYNUCLEINA (PAN 408 – PAN 527)

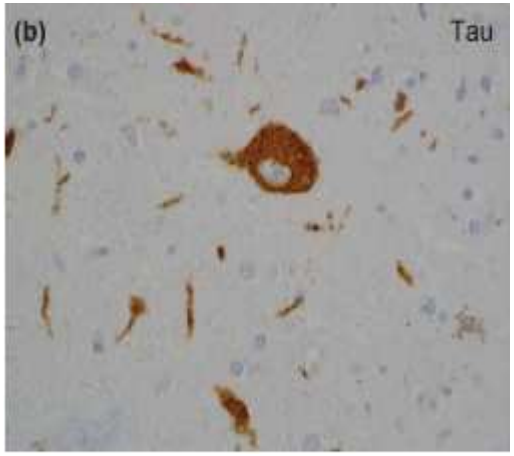
INIBITORI TRIPEPTIDICI DELLA CASPASI (ZVADfmk)

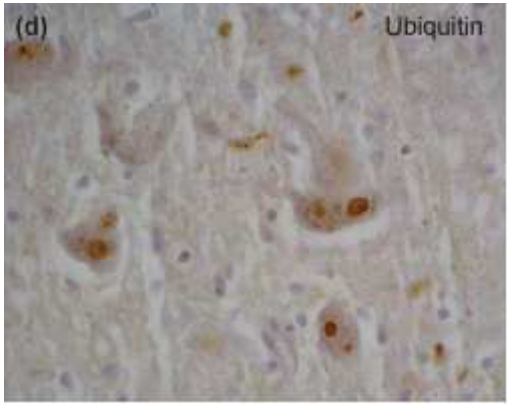
Methodology article

Open Access

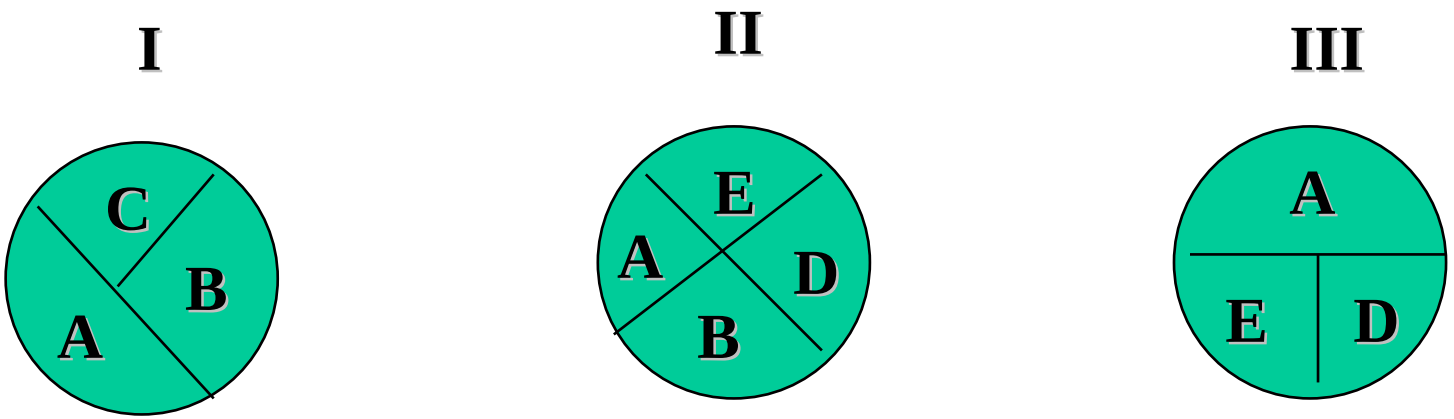
Joint analysis of two microarray gene-expression data sets to select lung adenocarcinoma marker genes

Hongying Jiang[†1], Youping Deng[†2], Huann-Sheng Chen[3], Lin Tao[3], Qiuying Sha[3], Jun Chen[2], Chung-Jui Tsai[1] and Shuanglin Zhang[*3]





A GENERAL MODEL OF CAUSATION



Three sufficient causes of a disease

A “sufficient” cause which means a complete causal mechanism, can be defined as a set of minim conditions and events that inevitably produce disease; “minimal” implies that all conditions or events are necessary

(KY Rothman and S Greenland 1998)