

Recent developments in

U **Parkinson's  
Disease Genetics** B

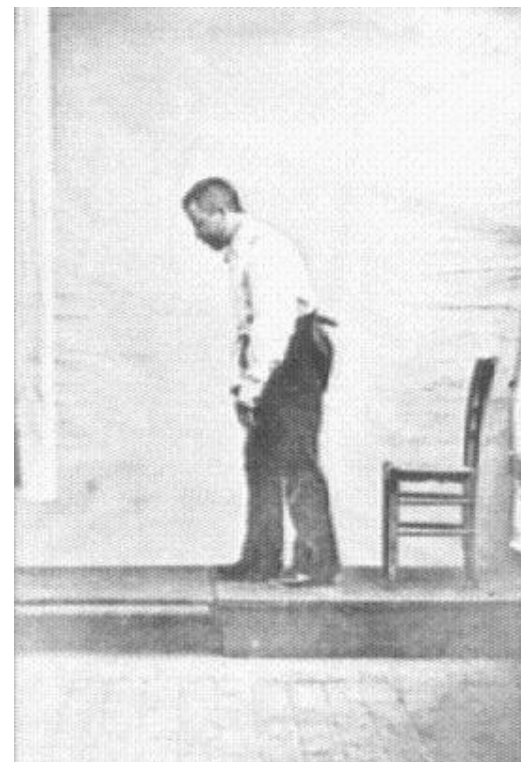
Karen E Morrison

Professor of Neurology, University of Birmingham,  
Consultant Neurologist, University Hospitals Birmingham

# Questions in Parkinson's Disease

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- What causes PD ?
- How can PD best be treated ?
- How can the onset of PD be prevented or delayed?
- How can we better target therapies
  - to those who will benefit most?
  - to minimise side effects?





PD GEN - one of 13 disease specific DNA collections in the UK ( 2001 - 2004 )



**Alzheimer's disease**

Breast cancer

Glomerulonephritis

Unipolar depression

Acute leukaemia

Type 2 diabetes

Coronary artery disease

Asthma & eczema

**Multiple sclerosis**

**Parkinson's disease**

Hypertension

Colorectal cancer

Macular degeneration

# PD GEN - add on study to PD MED/ PD Surg/ PD Rehab

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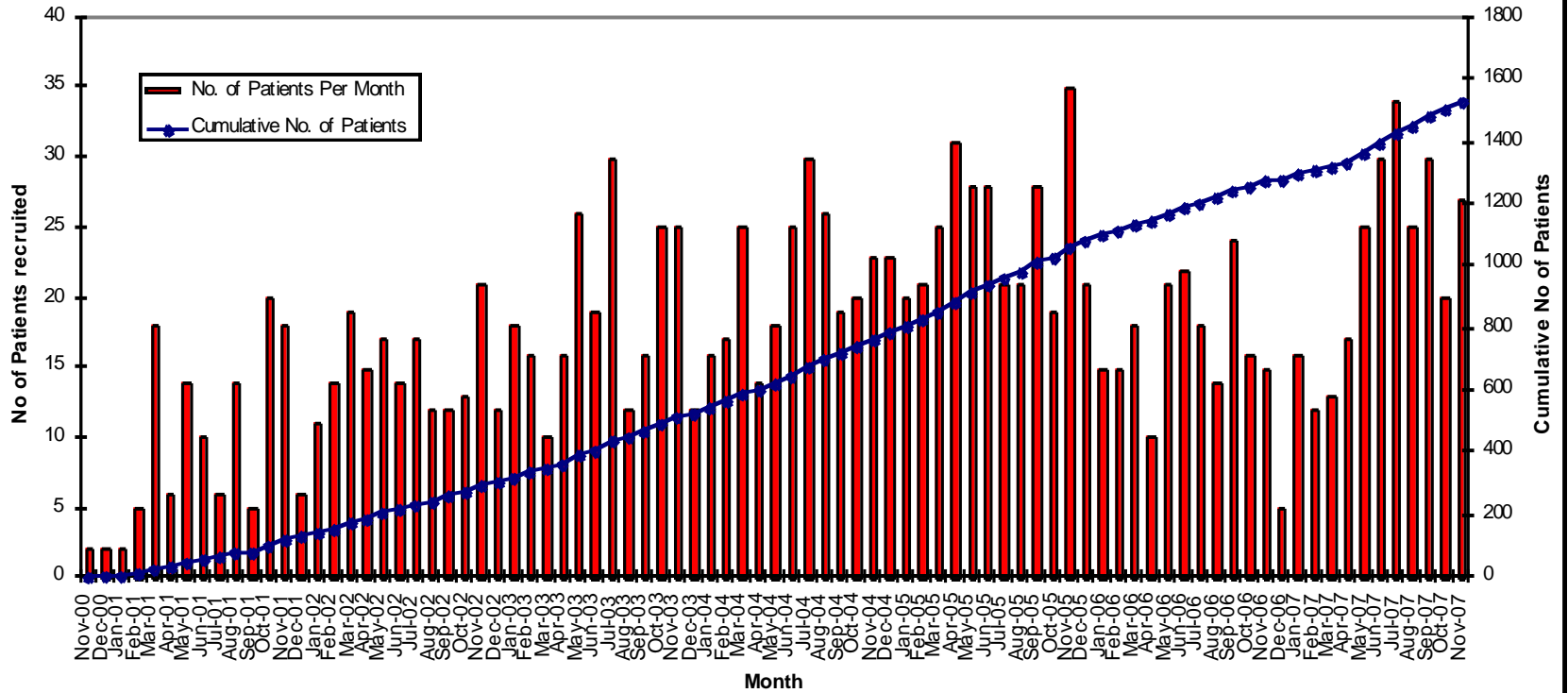
## Aims

- To collect **DNA samples** and **epidemiological data** from PD patients enrolled in PD MED, PD SURG and carers/spouses as controls

1000 PD patients 1000 controls

- To make this collection available for research

### Patients Recruited into PD MED



# Current numbers



PD patients: 1111

Controls: 588

Our University: a community where students, partners, alumni, staff and our research create international impact

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## University recruits 1000th patient to Parkinson's DNA Bank

Posted on Monday 15th November 2010

The University of Birmingham has recruited its 1,000th patient to PD GEN, a Parkinson's Disease DNA Bank being created by neurologists at the School of Clinical and Experimental Medicine.



Staff from the Birmingham Clinical Trials Unit and CEM

Parkinson's affects around 100,000 patients in the United Kingdom and is the most common neurodegenerative condition after Alzheimer's disease. With an exponential rise in its prevalence with age, its incidence is likely to significantly rise in the UK over the next 20 years.



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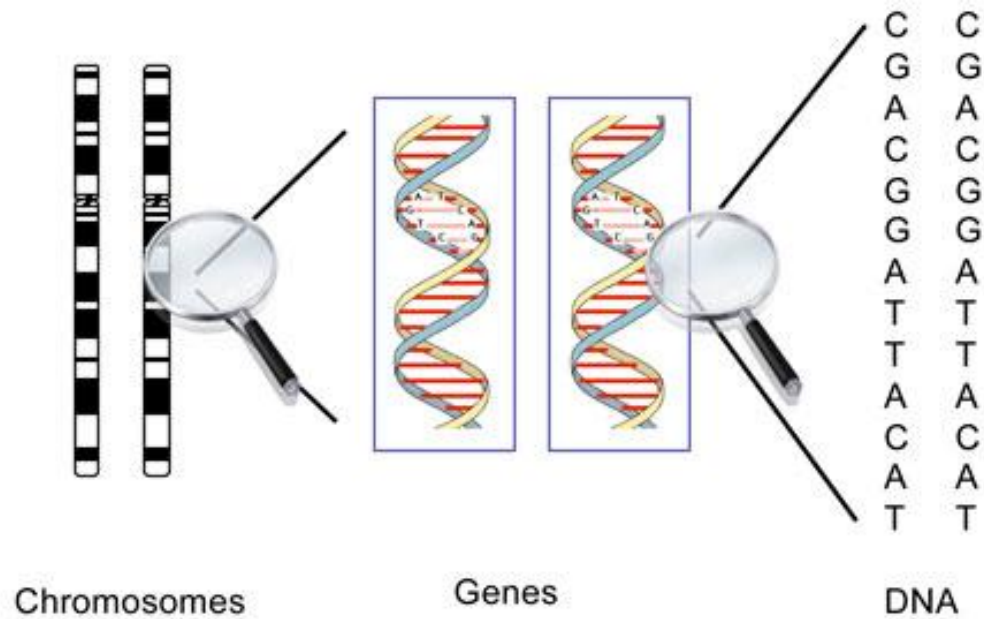
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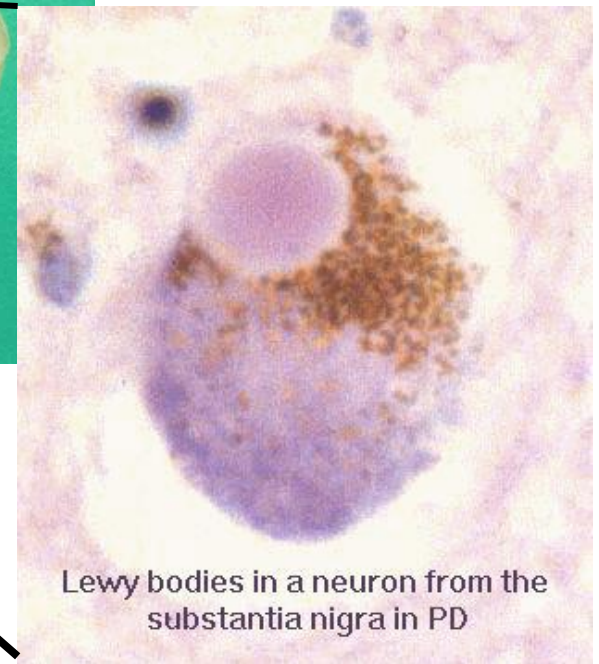
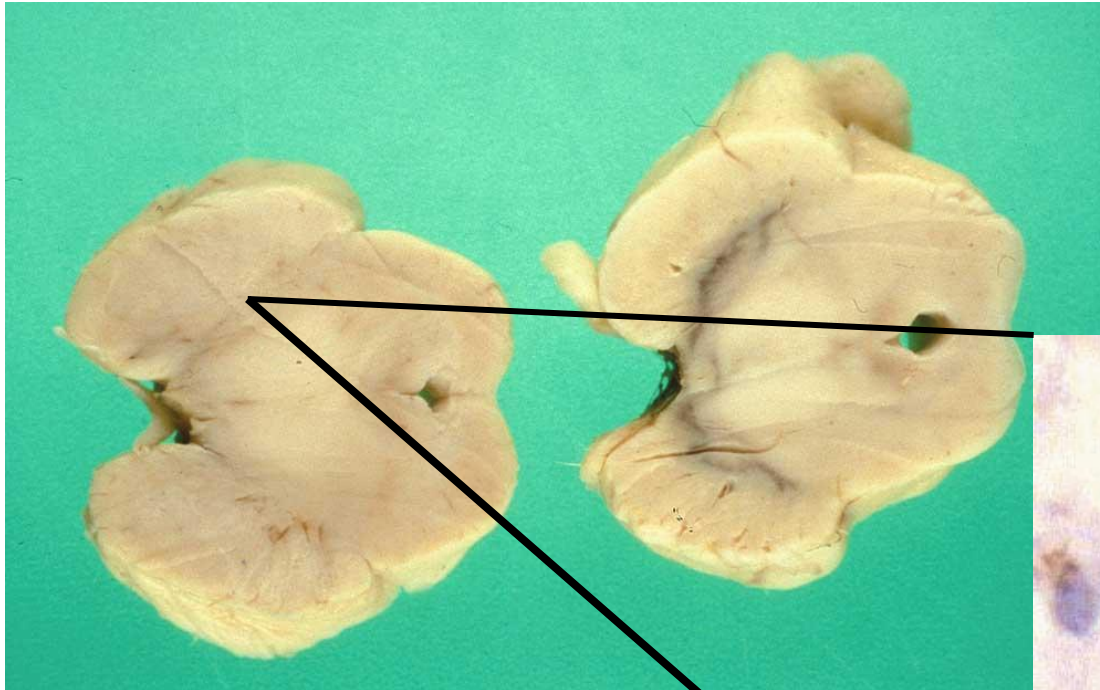
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# Parkinson's disease genetics

- what's new ?



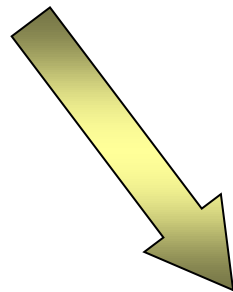
# Why study genetic factors in PD ?



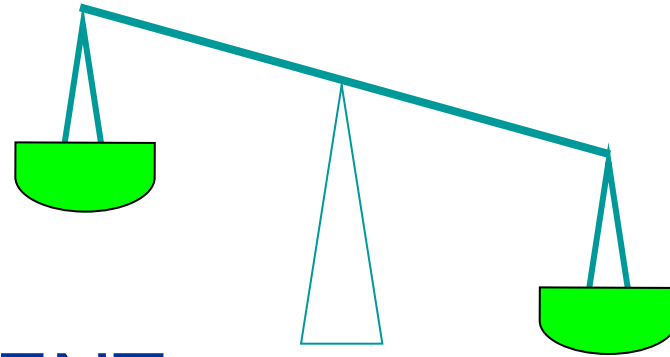
Lewy bodies in a neuron from the substantia nigra in PD

# Why study genetic factors in PD ?

- To inform about underlying disease mechanisms
- To lead to development of new therapies
- To better target drugs to individual patients



**BENEFIT FOR PD PATIENTS**



## ENVIRONMENT

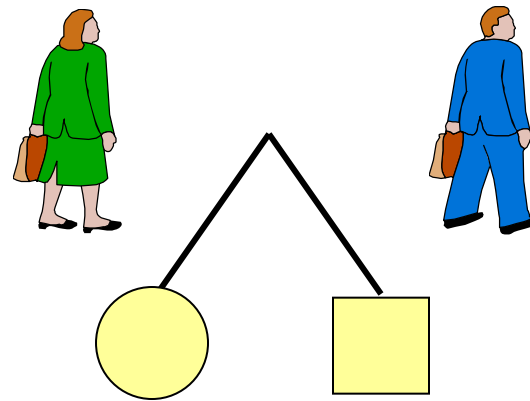
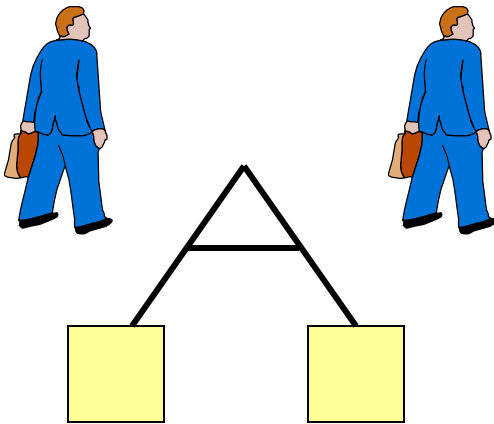
MPP<sup>+</sup>  
viral agents  
rural living  
wood mills  
well water  
Mn, cyanide  
pesticides  
smoking  
caffeine

## GENES



# Is PD a genetic disease?

Compare concordance in *monozygotic* v *dizygotic* twins



# Is PD a genetic disease?

- Is there an increased risk of PD in siblings compared to the general population ?

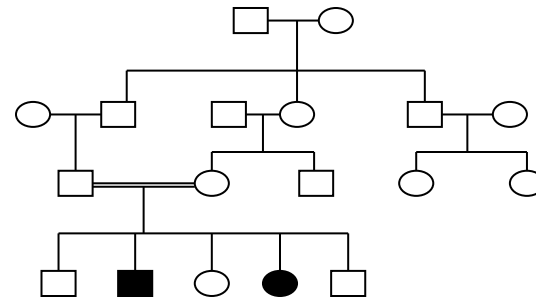
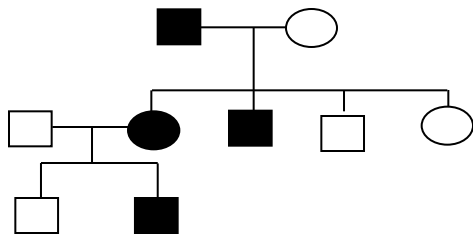
$$\lambda_S = \frac{\text{risk of sibling developing PD}}{\text{background risk of PD in the population}}$$

$$\lambda_S = 2 - 3 \text{ for PD}$$

$\lambda_S$ type 2 diabetes	3 - 4
rheumatoid arthritis	5 - 10
bipolar disorder	7 - 10
Crohn's	17 - 35

# Is PD a genetic disease?

- Most PD occurs in families without a previous history of the disease
- Sometimes (rarely) the disease clearly ‘runs in families’

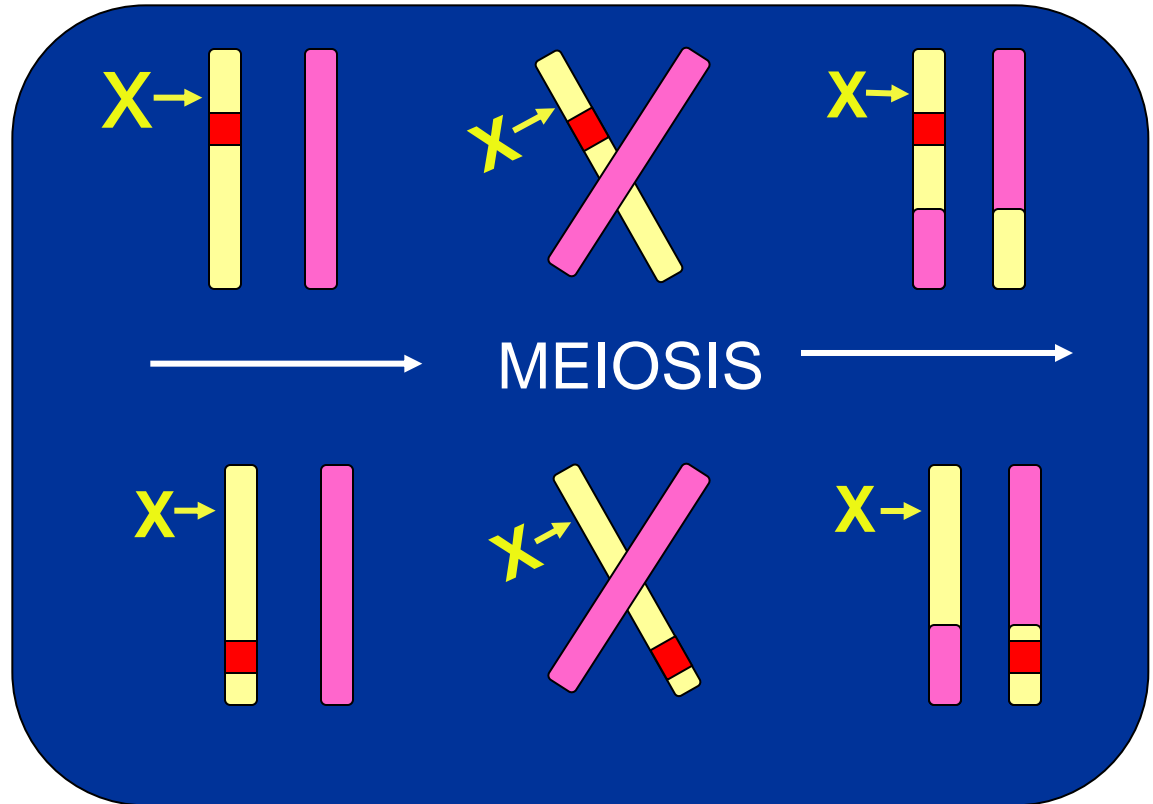


# Genetic linkage analysis

## Requirements

Families with disease

Genetic markers

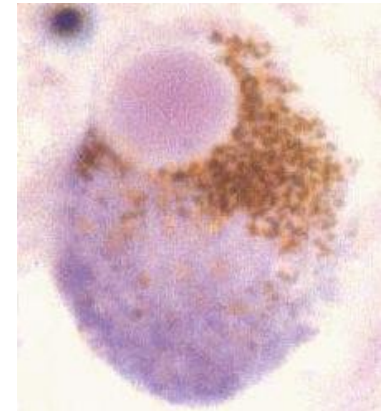


Statistical analysis of cross-over events between disease and marker

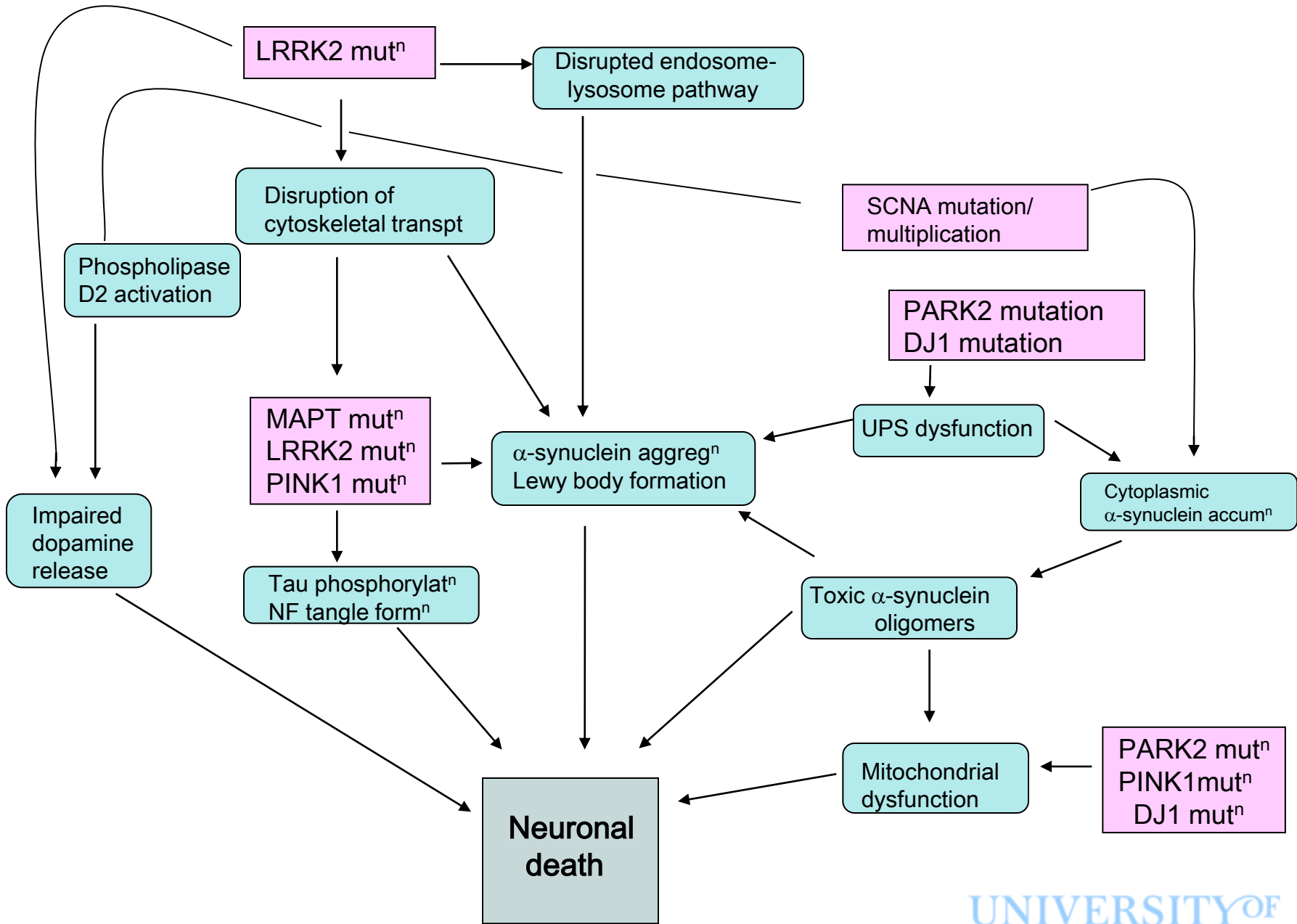


Fig 1. Centuri kindred pedigree as of January 1, 1996. The 2 individuals in Generation I are the earliest known common ancestors of all 60 affected individuals. Their years of birth are unknown, but their 2 known children (Generation II) were born in 1722 and 1726. There are no medical data for Generations I through V. Generations X through XII are not shown. Generation X included 3 affected individuals. For Generations VI through IX, open symbols represent absence of parkinsonism by history or examination. The mean age of individuals in Generation IX is approximately 50, suggesting that that generation has realized about half of its PD risk to date.

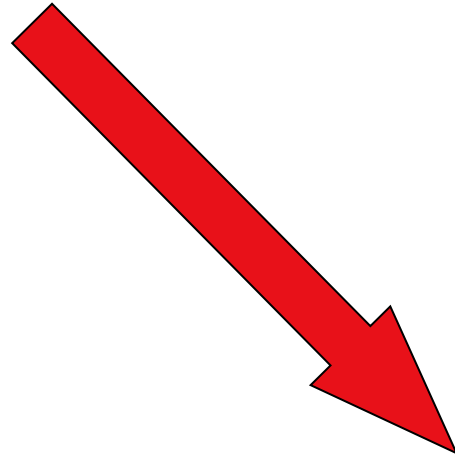
61 individuals,  
5 generations



Name	Location	Gene	Inheritance
Park 1	4q21-23	Alpha synuclein	AD
Park 2	6q25.2-27	Parkin	AR
Park 3	2p13	?	AD
Park 4	4p15	?	AD
Park 5	4p14	UCH-L1	AD
Park 6	1p35-36	PINK1	AR
Park 7	1p36	DJ1	AR
Park 8	12p11.2-q13.1	LRRK2	AD
Park 9	1p36	?	AR
Park 10	1p32	?	AR
FTDP-17	17q21-23	Tau	AD

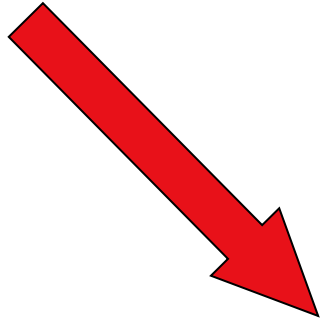


Importance of finding gene defects in rare familial pedigrees



Gain information on disease mechanism  
of relevance in the common sporadic disease

## Importance of finding gene defects in rare familial pedigrees



Variants in these genes may act  
as susceptibility factors  
in more common sporadic disease

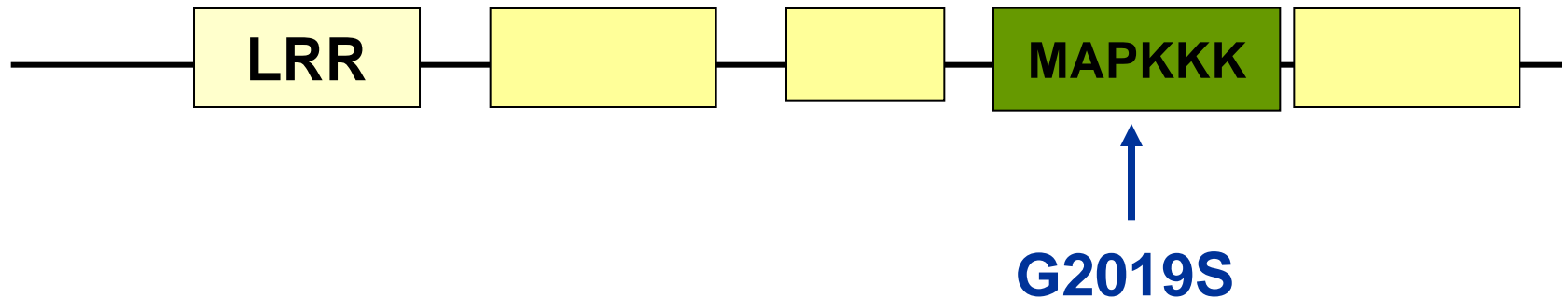
# LRRK2 - dardarin 12p12 PARK 8

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First linked in a Japanese family

- asymmetrical, late onset, L-DOPA responsive PD

Mutations identified in AD PD families in 2004



## **Gly2019Ser**

**0.5 - 2% of sporadic PD cases**

**5% of familial PD**

**Ashkenazi Jews and N African Arabs**  
**19 - 30% of PD**

Penetrance - 17% at 50 yrs, 85% at 70 yrs

Pathology - mainly Lewy body disease;  
rarely NF tangles and/or nigral neuronal loss

Phenotype - typical late onset PD

# Glucocerebrosidase (GBA) mutations in PD

Homozygous loss of function of GBA causes Gaucher's disease

Increased incidence of PD observed in relatives of Gaucher's disease patients

( Sidransky et al, *NEJM* 2009, **361 (17)**: 1651-1056)

Heterozygous GBA mutations are a risk factor for developing PD

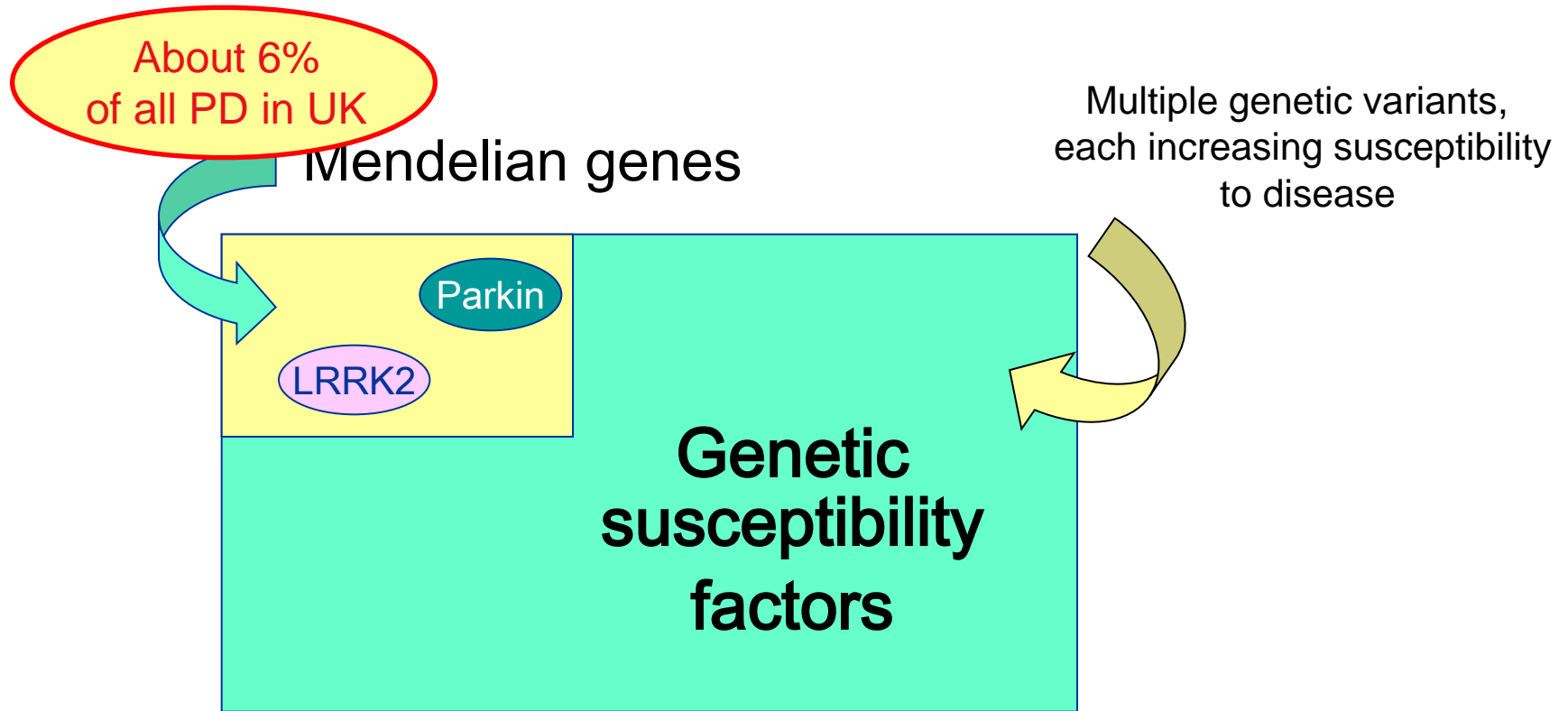
Ashkenazi Jews with PD

– 30% chance of carrying GBA or LRRK2 mutation

UK PD patients – overall 4% have GBA mutations

# Are there genetic susceptibility factors in PD ?

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# Certain DNA variants may increase our susceptibility to disease



ccgctacagctgaacct

no ↑ risk

ccgcta**a**agctgaacct

slightly ↑ risk

ccgcta**a**agctgaat**t**ct

higher risk ↑↑

ccgctacagctgag**g**cct

no ↑ risk

# Association studies in PD

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Compare the occurrence of a particular factor in individuals with the disease to that in controls without the disease

	X	Y
PD patients	a	b
Controls	c	d

$\chi^2$  analysis

$P < 0.05$

Null hypothesis: “*There is no difference in the distribution of X and Y in pats v controls*”

# Genome wide association studies in PD

**Tag SNPs:** maximise amount of variation captured per SNP

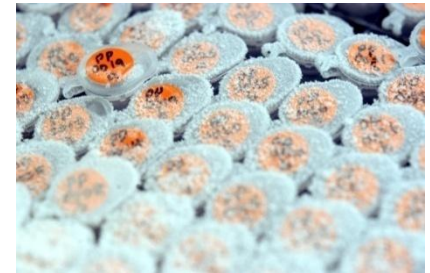
**Random SNPs**

**Combined:** random SNPs with custom tag sets

**Functional:** polymorphic nsSNPs or SNPs focused on genes

Markers

Genotyping  
platform



Samples

Analysis

# Will GWAS approaches be of value in PD ?

? Sufficient number of samples available

**YES**

Depends on the number of variants conferring increased risk

Depends on magnitude of effects of those variants

Depends on interactions – gene/gene, gene/environment

**3,000 cases, 3,000 controls** for 80% power to detect common alleles that associate with disease with OR >1.3

## Will GWAS be of value in PD ?

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Sufficient number of samples available

**YES**

? Sufficient 'genetic component' to PD

**YES**

? Heterogeneity

**Uncertain**

? If PD is caused by multiple rare variants/genomic rearrangements

**Uncertain**

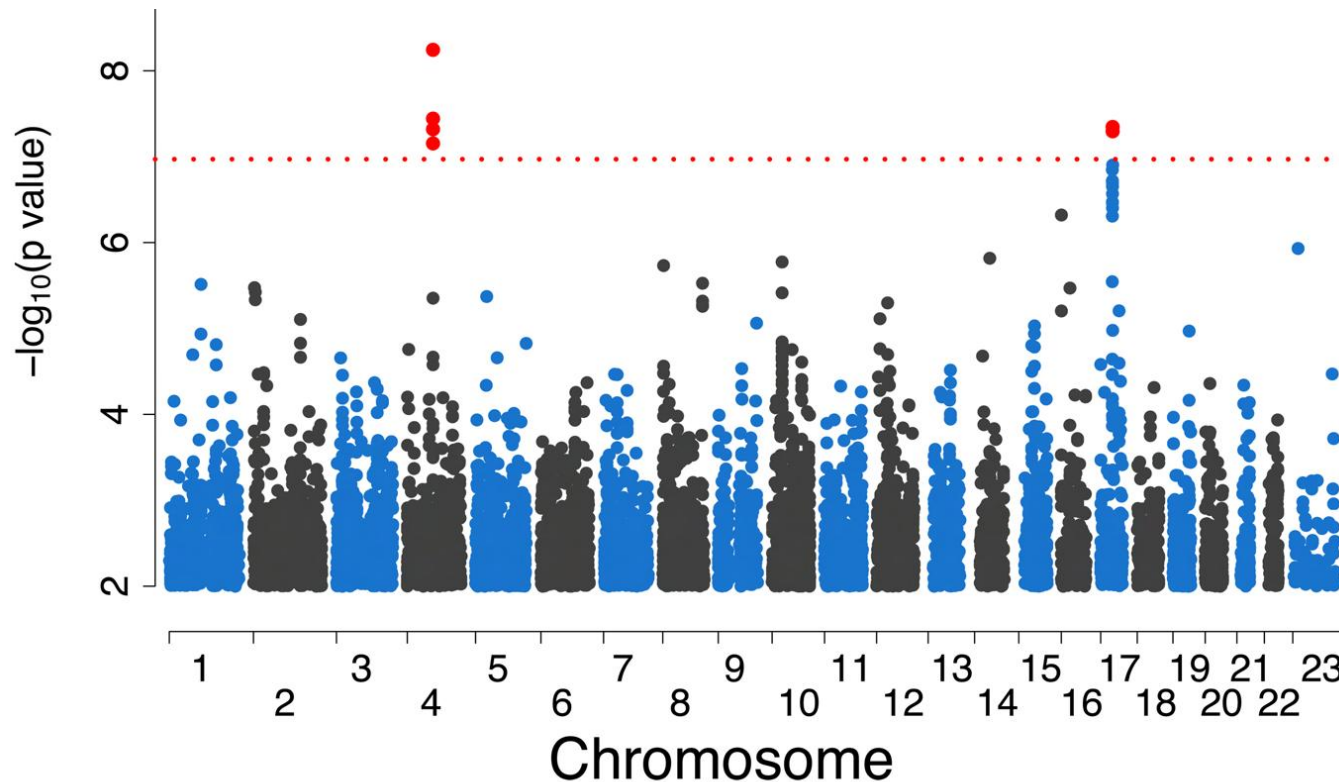
# Results of genome wide association studies in PD

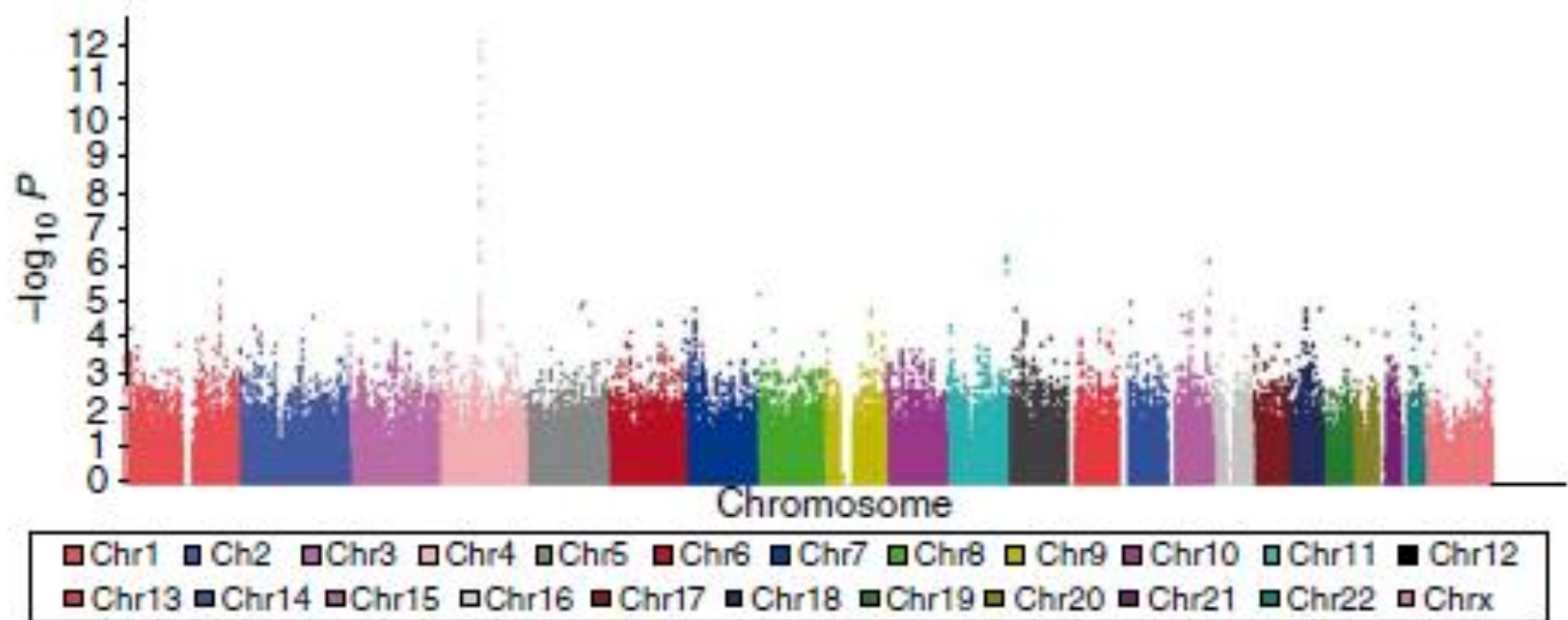
First reasonably large GWAS in PD published in 2009

Simon-Sanchez et al - 1713 European PD pats/ 3,978 controls

Satake et al – 2,011 Japanese cases and 18,381 controls

*“... a milestone for PD genetics”*





SCNA, 4q22 – significant association in both populations

SNPs in MAPT region – only significant in European population

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SNP near LRRK2, 12q12 – significant in Japanese pats, not in Europeans

New locus on chromosome 1q32 – significant in Japanese,  
replicated in European pats

New locus on chromosome 4p15 - BST1 - in Japanese pats

# Dissection of the genetics of Parkinson's disease identifies an additional association 5' of *SNCA* and multiple associated haplotypes at 17q21

The UK Parkinson's Disease Consortium and The Wellcome Trust Case Control Consortium 2†

Received July 13, 2010; Revised October 8, 2010; Accepted October 26, 2010

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We performed a genome-wide association study (GWAS) in 1705 Parkinson's disease (PD) UK patients and 5175 UK controls, the largest sample size so far for a PD GWAS. Replication was attempted in an additional cohort of 1039 French PD cases and 1984 controls for the 27 regions showing the strongest evidence of association ( $P < 10^{-4}$ ). We replicated published associations in the 4q22/*SNCA* and 17q21/*MAPT* chromosome regions ( $P < 10^{-10}$ ) and found evidence for an additional independent association in 4q22/*SNCA*. A detailed analysis of the haplotype structure at 17q21 showed that there are three separate risk groups within this region. We found weak but consistent evidence of association for common variants located in three previously published associated regions (4p15/*BST1*, 4p16/*GAK* and 1q32/*PARK16*). We found no support for the previously reported SNP association in 12q12/*LRRK2*. We also found an association of the two SNPs in 4q22/*SNCA* with the age of onset of the disease.

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About 500 PD GEN samples – their first use

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# Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies



International Parkinson Disease Genomics Consortium\*

## Summary

**Background** Genome-wide association studies (GWAS) for Parkinson's disease have linked two loci (*MAPT* and *SNCA*) to risk of Parkinson's disease. We aimed to identify novel risk loci for Parkinson's disease.

**Methods** We did a meta-analysis of datasets from five Parkinson's disease GWAS from the USA and Europe to identify loci associated with Parkinson's disease (discovery phase). We then did replication analyses of significantly associated loci in an independent sample series. Estimates of population-attributable risk were calculated from estimates from the discovery and replication phases combined, and risk-profile estimates for loci identified in the discovery phase were calculated.

**Findings** The discovery phase consisted of 5333 case and 12019 control samples, with genotyped and imputed data at 7 689 524 SNPs. The replication phase consisted of 7053 case and 9007 control samples. We identified 11 loci that surpassed the threshold for genome-wide significance ( $p < 5 \times 10^{-8}$ ). Six were previously identified loci (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK* and *LRRK2*) and five were newly identified loci (*ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11*, and *CCDC62/HIP1R*). The combined population-attributable risk was 60.3% (95% CI 43.7–69.3). In the risk-profile analysis, the odds ratio in the highest quintile of disease risk was 2.51 (95% CI 2.23–2.83) compared with 1.00 in the lowest quintile of disease risk.

*Lancet* 2011; 377: 641–49

Published Online

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DOI:10.1016/S0140-

6736(10)62345-8

See Comment page 613

\*Members listed at end of paper

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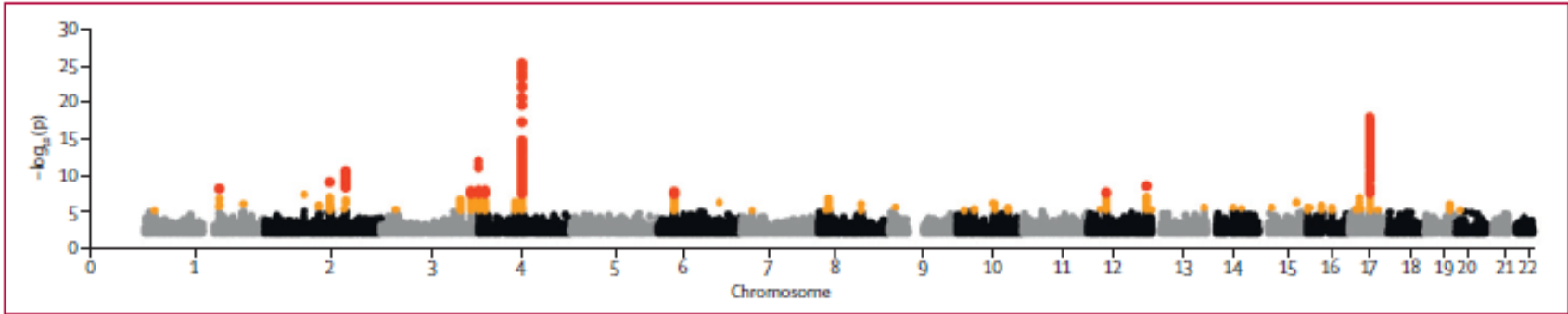
Drive, Bethesda, MD 20837, USA

singleton@mail.nih.gov

Meta-analysis of 5 GWAS studies – 2 X USA, UK, Germany, France

Authors -144

# Discovery Phase, 5333 cases, 12019 controls



**Figure 1: Manhattan plot of Parkinson's disease associations for all SNPs in the discovery phase**

p values from fixed-effects meta-analysis for 7 689 524 SNPs successfully imputed or genotyped in at least two individual datasets. Genomic inflation factor=1.035. Red points=SNPs with  $p < 5 \times 10^{-8}$ . Orange points=SNPs with p values ranging from less than  $1 \times 10^{-4}$  to  $5 \times 10^{-4}$ . Regions containing red points were followed up in replication analyses. SNP= single nucleotide polymorphism.

11 loci passed threshold for genome wide significance ( $p < 5 \times 10^{-8}$ )

	C	Position (bp)	MAF in discovery phase	Minor/major alleles	Candidate gene
	1	154105678	0.02	T/C	SYT11
	2	135308851	0.19	A/G	ACMSD
	2	168825271	0.13	T/G	STK39
	3	184303969	0.14	A/G	MCCC1/LAMP3
	4	911311	0.28	C/G	GAK
	4	15346199	0.45	C/A	BST1
	4	90856624	0.39	G/A	SNCA
	6	32588205	0.15	G/A	HLA-DRB5
	12	38907075	0.21	G/C	LRRK2
	12	121862247	0.46	A/G	CCDC62/HIP1R
	17	41070633	0.22	A/G	MAPT

★ 6 confirmed associations  
5 new associations



# Population attributable risk estimates

	p value	AUC	Risk quintile OR (95%CI)				
			First (reference group)	Second	Third	Fourth	Fifth
USA	$<2 \times 10^{-28}$	0.584	1.00	1.49 (1.25-1.78)	1.67 (1.40-2.00)	1.90 (1.59-2.27)	2.25 (1.88-2.70)
UK	$<2 \times 10^{-28}$	0.631	1.00	1.63 (1.27-2.08)	2.26 (1.77-2.88)	2.65 (2.09-3.38)	3.30 (2.60-4.21)
Germany	$1.44 \times 10^{-8}$	0.69	1.00	1.16 (0.86-1.57)	1.55 (1.14-2.11)	1.68 (1.23-2.29)	2.06 (1.51-2.82)
France	$6.15 \times 10^{-8}$	0.644	1.00	1.24 (0.72-2.16)	2.13 (1.26-3.66)	2.84 (1.68-4.88)	4.31 (2.51-7.55)
Netherlands	$8.34 \times 10^{-4}$	0.576	1.00	1.21 (0.74-2.00)	1.12 (0.68-1.84)	1.50 (0.93-2.42)	1.89 (1.17-3.07)
Combined	$<2 \times 10^{-28}$	0.63	1.00	1.43 (1.27-1.62)	1.77 (1.55-1.99)	2.03 (1.80-2.32)	2.51 (2.23-2.83)
Cases (%)	..	..	886 (39.00%)	1069 (47.13%)	1185 (52.16%)	1268 (55.93%)	1394 (61.17%)

Combined analyses showed low heterogeneity of effect (Cochran's Q  $p > 0.01$ ). AUC=area under curve, indicated by the c index from receiver operator curves. OR=odds ratio.

'Strong' genetic component to PD

Combined estimate for contribution across all loci - 60.3 % ( CI 43.7 – 69.3)

MAPT/SCNA - 25.6 %

ACMSD, STK39, MCCC1/LAMP3, CCDC62/HIP1R - 46.7%

# PD GEN sample use in Early Onset PD

3.6% of patients have disease onset before 45 years

If young onset, there is a higher familial recurrence risk

Parkin, PINK1, DJ-1

- Analysis of recessive genes in UK young onset cases
- Homozygosity mapping – to identify new recessive PD genes

- Dr Huw Morris, Cardiff

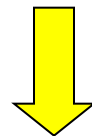


X - genetic variant/ SNP

■ - factor increasing susceptibility to PD

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How does X  
relate to increased  
PD susceptibility?



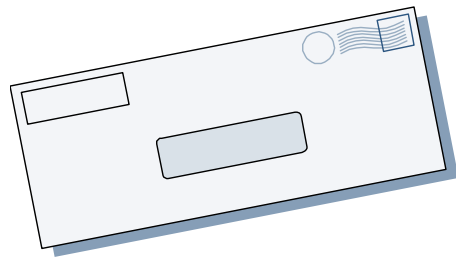
**FUNCTIONAL STUDIES**

(J. Hardy and A Singleton, *NEJM* **360**;17: 1759-1769)

# LOGISTICS OF PD GEN

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- Patients need to be recruited to PD MED/ PD SURG/ PD REHAB
- Introduce and inform about PD GEN
- Obtain PD GEN 'pack' -



info sheets, *consent form*  
environmental questionnaire  
sample bottles, needle, collar  
packaging  
labels  
postage prepaid addressed envelope

DeNDRON

- Post to Lab

## PD GEN team:

Karen Morrison  
Carl Clarke  
Keith Wheatley

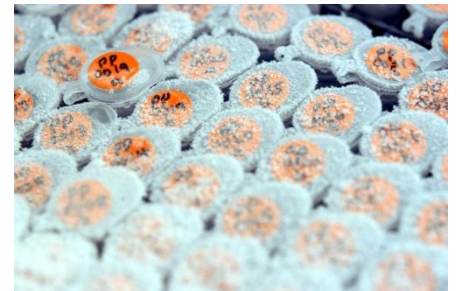
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