



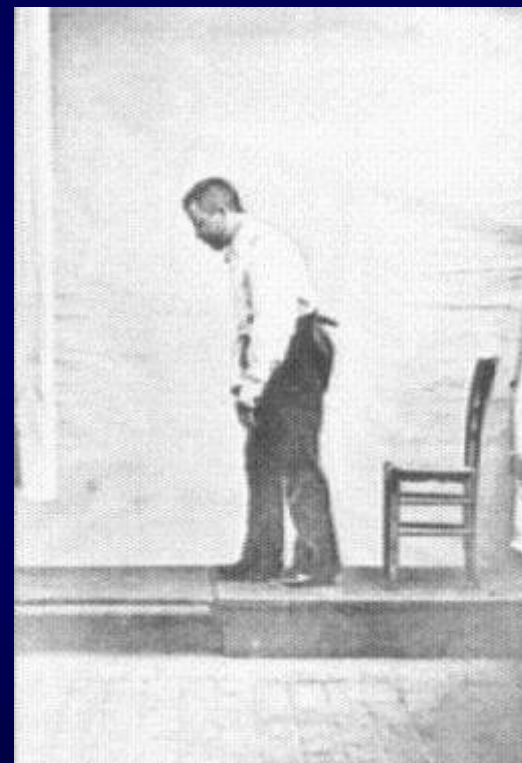
PD GEN - What is the point?

Karen E. Morrison

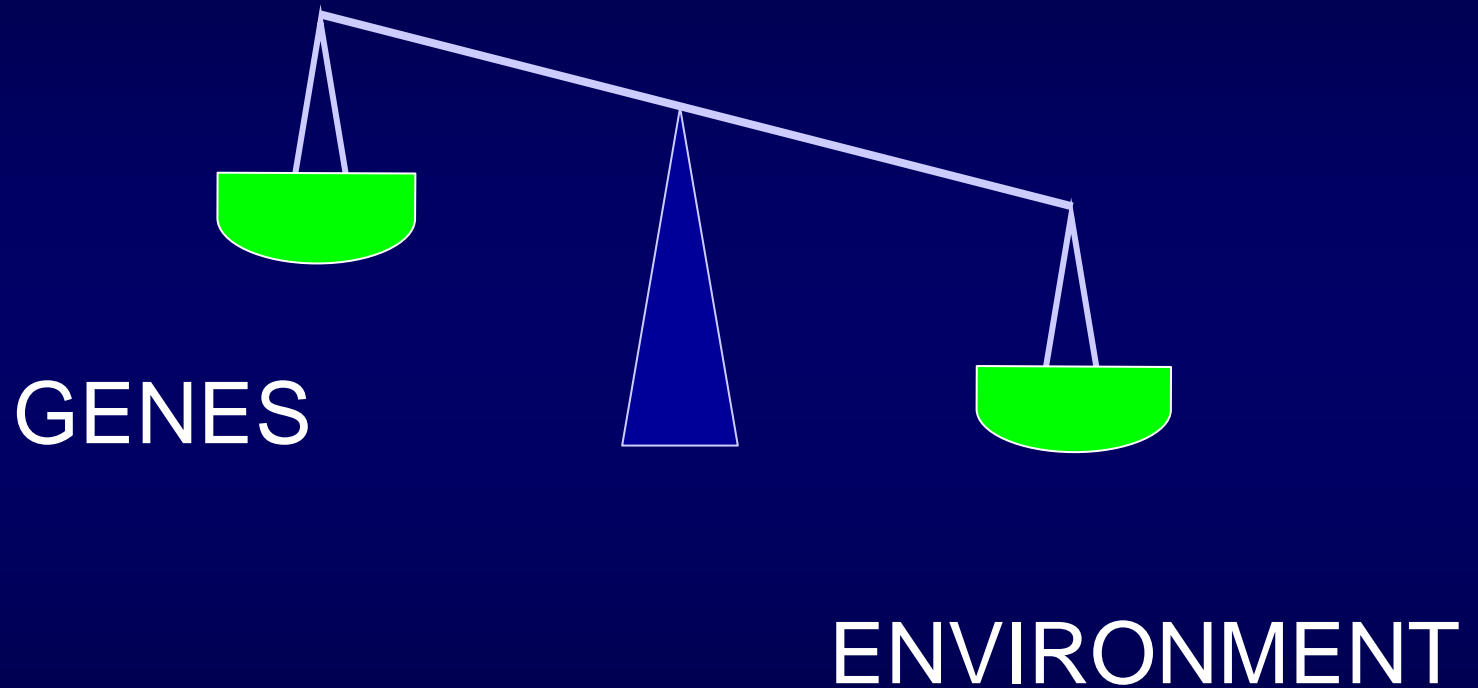
Professor of Neurology, University of Birmingham
Honorary Consultant neurologist, UHB NHS Foundation Trust

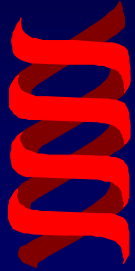
Questions in Parkinson's Disease

- 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?

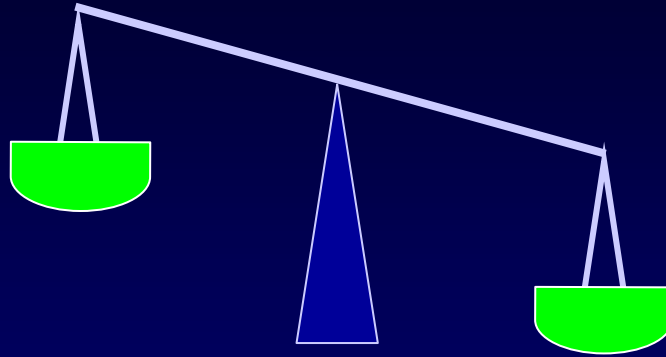


What causes PD ?





GENES



ENVIRONMENT

MPP⁺

viral agents
rural living
wood mills
well water
Mn, cyanide
pesticides

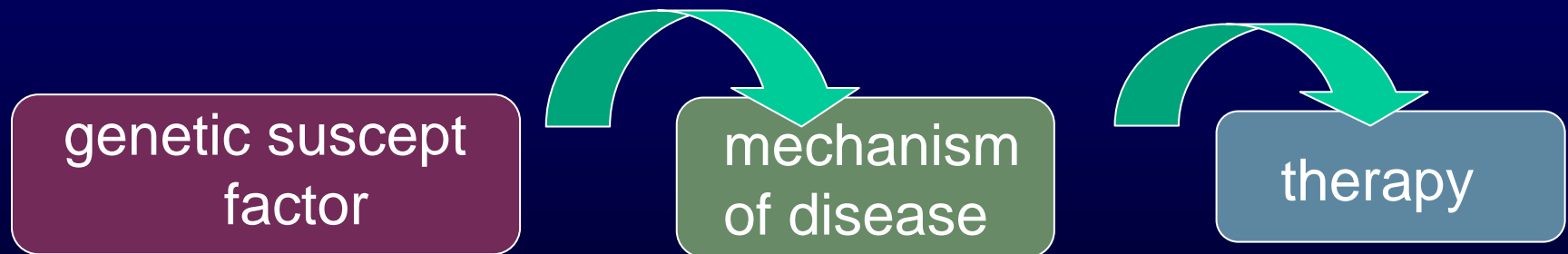
smoking

caffeine

Genetic susceptibility to PD

- likely to result because a number of different genetic factors increase likelihood of developing the disease

Aim to **IDENTIFY** genetic susceptibility factors and determine their **FUNCTION**, to gain knowledge of disease **MECHANISM** and aid **THERAPY** development



Is PD a genetic disease?

PD can 'run in families'



- Mendelian forms - autosomal dominant
autosomal recessive
- genetic susceptibility factors

Genetic linkage analysis

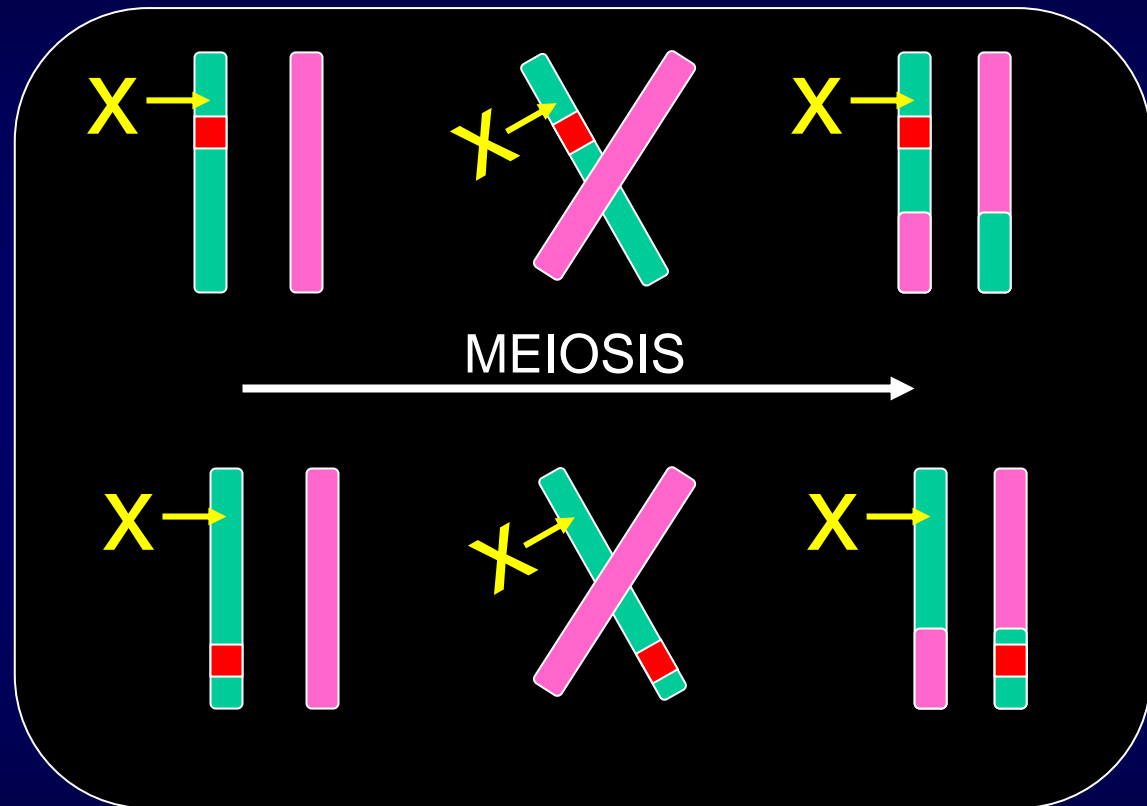
Requirements

Families with disease

Polymorphic markers

Mode of inheritance

Penetrance



Statistical analysis of cross-over events between disease and marker

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

Genetic causes of PD

Dominant α synuclein

LRRK2

Recessive Parkin mutations

UCHL1 mutations

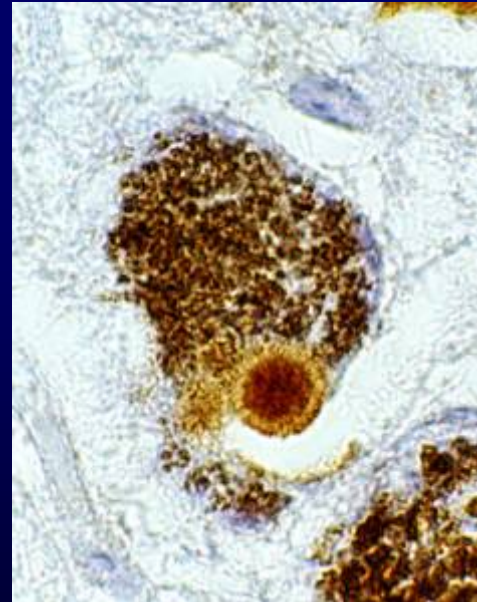
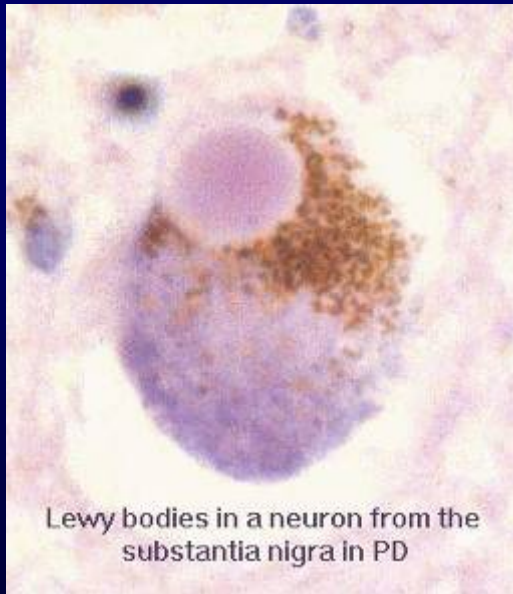
DJ-1 mutations

PINK1 mutations

α synuclein (SCNA)

3 mutations identified in a few pedigrees

6 families with de novo duplications/triplications of 4q21



SCNA mutation phenotype

Progressive L-DOPA responsive parkinsonism,
associated with cognitive decline,
autonomic dysfunction and dementia

SCNA triplication

- more rapid disease progression

Pathology – diffuse Lewy body disease,
nigral and hippocampal neuronal loss

Function of α synuclein

Synaptic plasticity

Vesicle trafficking

DA synthesis (inhib tyrosine hydroxylase)

Model organisms

Overexpression in yeast, human cells, worms, flies, mice, rats

- neurotoxicity, aggregation

Drosophila – loss of DA neurons, Lewy body-like inclusions,
and movt disorder ameliorated by L-DOPA/ DA agonists

? phosphorylation at serine 129 key in toxicity

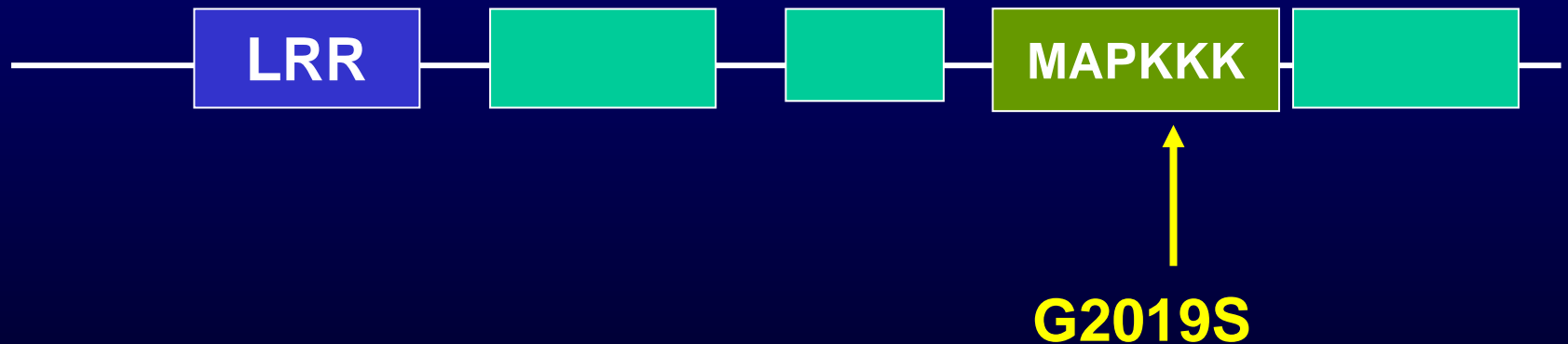
- geldanamycin

LRRK2 - dardarin 12p12 PARK 8

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

Function of LRRK2

- substrate binding, protein phosphorylation
protein-protein interactions

Expression - widespread

Member of RIP kinases - sensors of cellular stress

Dictyostelium homologue - encodes a protein required for assembly of myosin during chemotaxis

C. Elegans Irk-1 k.o. - chemosensory deficit

Mutant G2019S - increased activity of kinase domain

Genetic causes of PD

Dominant α synuclein

LRRK2

Recessive Parkin mutations

UCHL1 mutations

DJ-1 mutations

PINK1 mutations

Parkin PARK 2 AR

Juvenile, early onset disease
Dystonia, diurnal fluctuations
Response to low doses L-DOPA

Pathology - loss of DA neurons in SN, LC
no Lewy bodies/tangles

50% of familial juvenile and early onset disease
18% of sporadic disease < 50yrs

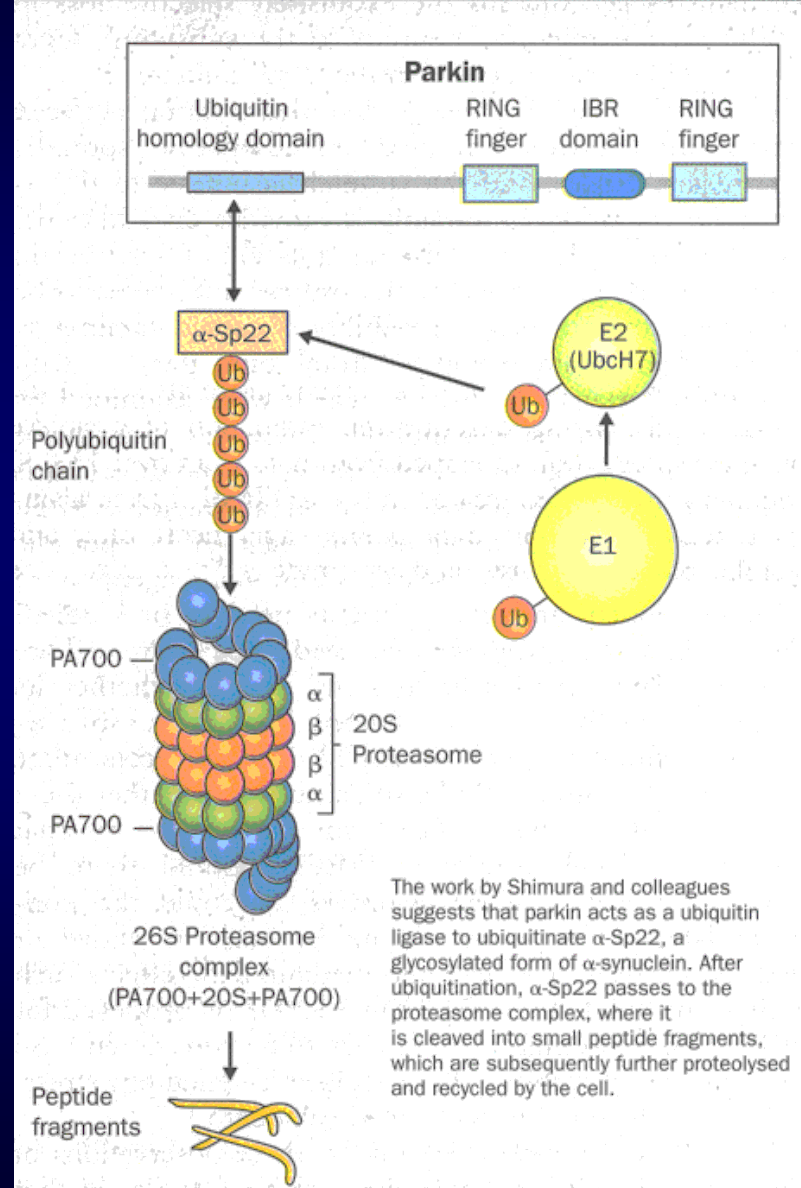
Parkin - functions

Is an E3 ligase -
conjugates ubiquitin to proteins
to target them for degradation

Drosophila and mouse loss of
function models
- suggests role in mitochondrial
dysfunction and oxidative stress

Overexpression
- ? neuroprotective

Interaction between parkin and synuclein



PINK 1

PARK 6

1p35-p36

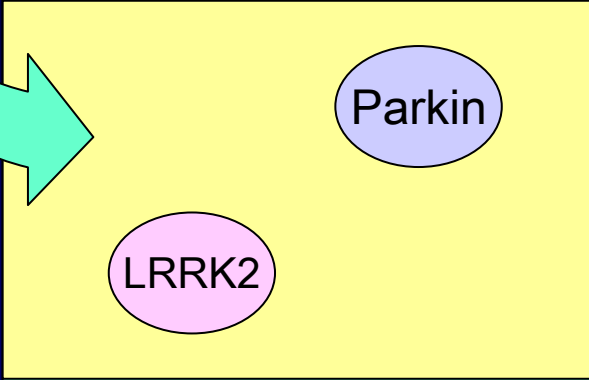
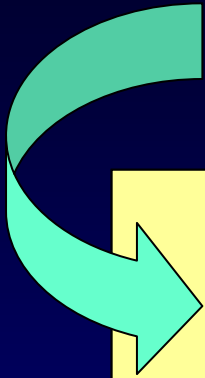
Mutations in 1 - 2% of early onset cases

Transcript encodes mitochondrial targeting motif
and protein kinase domain

WT PINK1 - protects neurons in culture from mitochondrial
dysfunction and apoptosis induced by various stressors

? Heterozygous PINK1 mutations can cause disease

Mendelian genes



Susceptibility factors

Genetic causes of PD

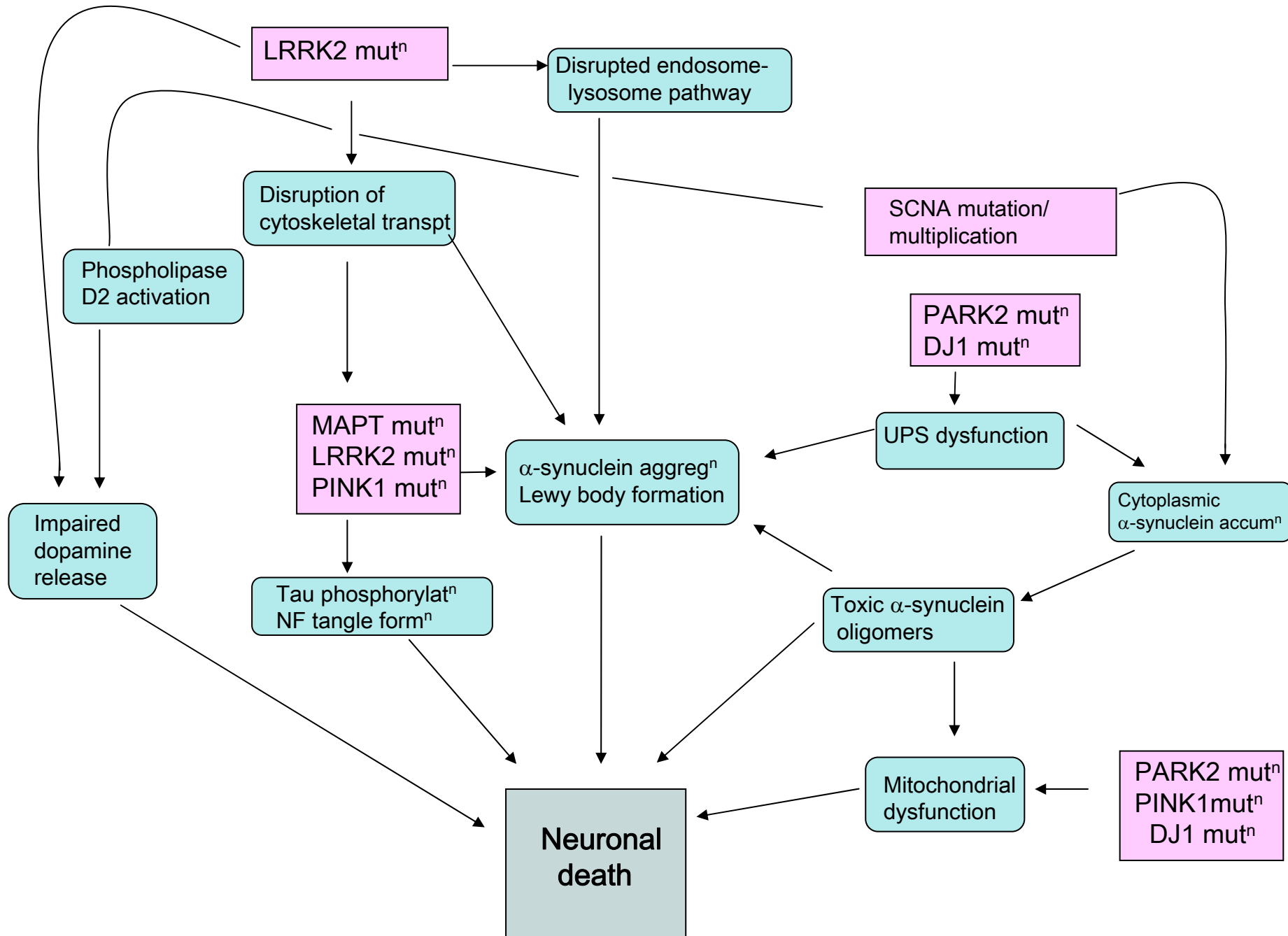
Genetic susceptibility factors in PD

SCNA

Common variant in promoter region leads to increased expression of SCNA and increased risk sporadic PD (needs further study)

Parkin

Heterozygous promoter and coding polymorphisms associated with susceptibility to late-onset PD

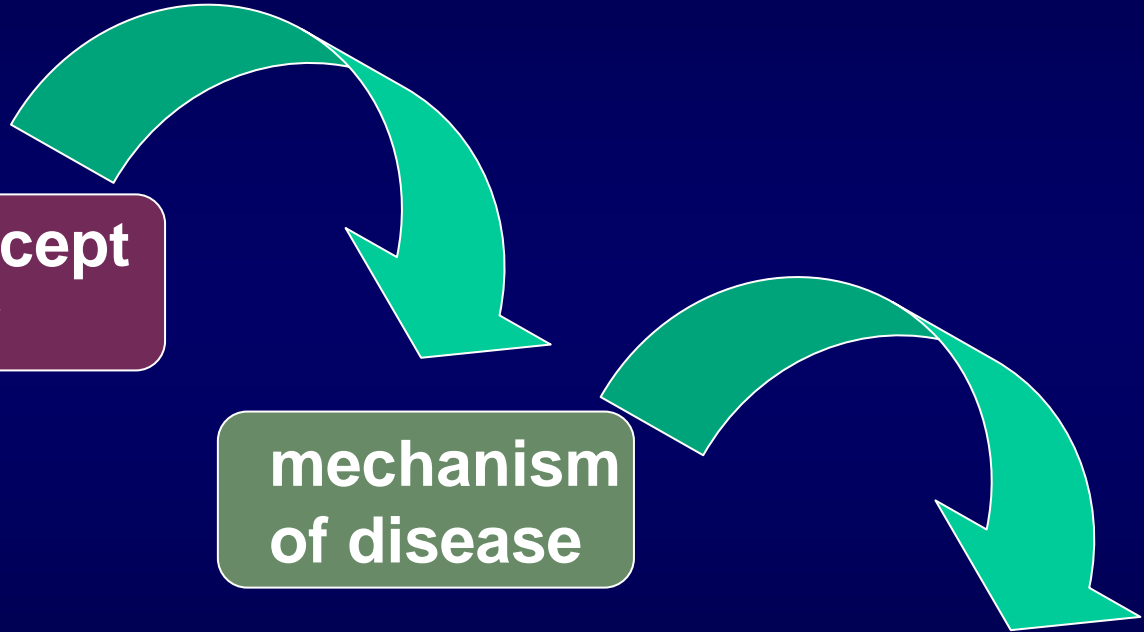


Genetic susceptibility to PD

genetic suscept
factor

mechanism
of disease

therapy



Targets for treatment

Reduce α synuclein

-in transgenic SCNA mice with siRNA

LRRK2 Gly2019Ser mutation

seems to increase kinase activity

? use compounds to inhibit kinases

PINK1/DJ1 - AR - strategies to replace wild type gene

Genetic susceptibility factors in PD

Genes mutated in mendelian forms of PD

Genes based on plausible functional hypotheses

Major difficulties with determining susceptibility loci

Sample size

Genetic heterogeneity

Phenocopies

Penetrance

Genotyping

**Need large/ very large
sample numbers**

COLLABORATION



Clinical Trials Unit
University of Birmingham

Tel: 0121-687-2315

Molecular Neurology Group
Institute of Biomedical Research
The Medical School
University of Birmingham
Edgbaston
Birmingham B15 2TT

Tel: 0121-414-3943

E-mail:
k.morrison@bham.ac.uk

LOGISTICS OF PD GEN

Recruit patients to PD MED/ PD SURG

Introduce and inform about PD GEN

Obtain PD GEN 'pack' -

info sheets, *consent form*

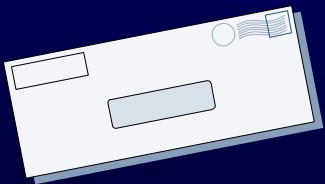
environmental questionnaire

sample bottles, needle, collar

packaging

labels

postage prepaid addressed envelope



Post to Lab