The Aetiology & pathogenesis of Parkinson's disease

Dr David Nicholl

Dept of Neurology,

Queen Elizabeth Hospital & City Hospitals, Birmingham

@bhammodis

THE UNIVERSITY OF BIRMINGHAM

Structure of this talk

- Background
  - Genetics of Parkinson's disease
    - Focusing on recent developments
  - Clinical relevance
    - What do I tell my patients?
    - Investigations

Sample type DNA Date Test Reported 18/01/18

REPORT OF DNA ANALYSIS

Next-generation sequencing (NGS) coverage:

100% of the coding exons (+/- 15 base pairs) of all genes in the panel were sequenced to a read depth of 30X or greater. The minimum depth of coverage was 52X.

Please contact the laboratory if further information is required.

NHNN Test Code: PRK1+PRK3

Methodology: Enrichment was performed with an Illumina custom Nextera Rapid Capture panel (PD Panel: Neurogenetics_NRC_v1.3) prior to next-generation sequencing on an Illumina MiSeq or HiSeq. NGS analysis is performed using an in-house pipeline. This test has a sensitivity of >95% at the 95% confidence interval for all sequencing over a depth of 30X. The sensitivity to detect insertions/deletions over 24 bp in length may be lower than this. All sequencing <10X is manually inspected.

The MLPA analysis is performed using the P051D1 kit from MRC-Holland and detects exonic deletions/duplications in SNCA (PARK1: exons 1-7), PARK2 (Parkin: all 12 coding exons and a probe in exon 39 of the LPA gene), PINK1 (PARK6: all 8 coding exons), PARK7 (DJ1: all 7 coding exons and a region 5' to exon 1), ATP13A2 coding exons 2 and 9, the Ala30Pro mutation in SNCA (PARK1) and the Gly2019Ser mutation in LRRK2 (PARK8).

The 'A' of the translation initiator ATG is numbered as +1. Mutation nomenclature used is according to current HGVS (Human Genome Variation Society) guidelines: www.hgvs.org/mutnomen/

Resources: www.genetests.org/; www.ncbi.nlm.nih.gov

The Neurogenetics Laboratory is UKAS accredited medical laboratory No.8040. Our accreditation currently covers any Sanger sequencing and MLPA analysis that contributes to this report (if performed). NGS sequencing is not UKAS accredited, however an application for this is under consideration.

Sample type DNA Date Test Reported 18/01/18

REPORT OF DNA ANALYSIS

Activation date: 28/11/2016

Reason for referral: Parkinson Disease (PD)

Type of Test: Diagnostic

Test performed: Next-generation sequencing (NGS) analysis of a panel of 7 genes involved in different forms of Parkinson Disease and MLPA gene dosage analysis of 3 genes. See below for a full list of genes and the footer of page 2 for the methodology.

Result: No pathogenic mutation detected

Interpretation: This result significantly reduces the likelihood that a mutation in the genes listed below is a cause of the clinical phenotype. It does not exclude large-scale rearrangements in the genes not targeted by the MLPA analysis, or mutations in other genes that may cause PD.

Comments: Please see page 2 of this report for details of the coverage of the genes targeted

Export PDF
Adobe Export PDF
Convert PDF Files to Word or Excel Online
Select PDF File
90477 16J10...K1+PRK3.pdf
Convert to
Microsoft Word (*.docx)
Document Language: English (U.S.) Change

How confident can we be with the diagnosis of Parkinson's disease?

- There is a diagnostic error rate
  - In primary care- ~50%
  - In movement disorders clinics ~10% (Hughes et al, 2001)
  - From imaging studies (Whone AL, et al. The REAL-PET study. Ann Neurol. 2003;54:93-101.); The Parkinson Study Group N Engl J Med 2004; 351:2498-2508)

Or what is my risk of PD?

How genetic is PD?

- 15% of PD patients have an affected relative (Gowers, 1893)
- twin studies (Tanner, 1998)
- large families
- Association studies ~813 studies…only 4 genes (SNCA, MAPT,LRRK2, PARK16) hold up….until GWAS (Dec 2009) http://www.pdgene.org/

pdgene.org

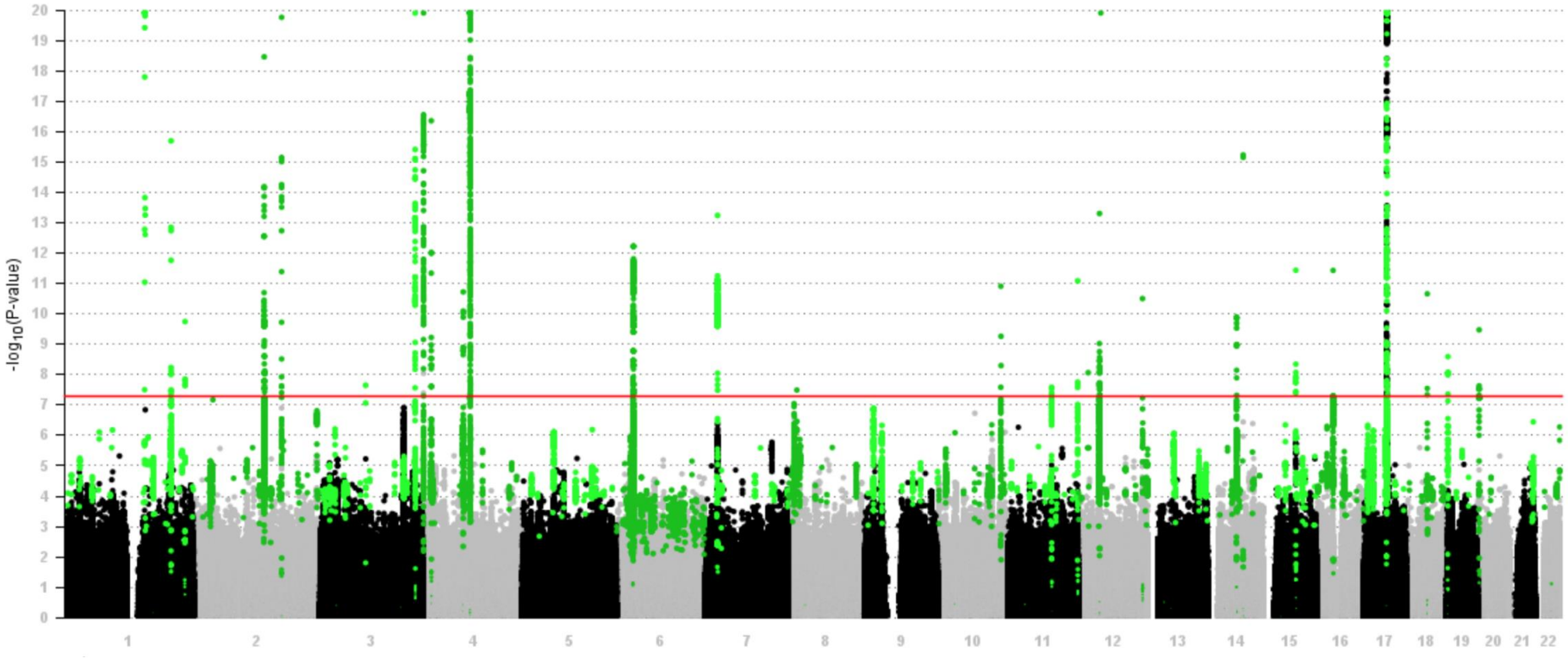
PDGene

PDGENE

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Top Results | MyMeta | GWAS | Links | About Us | Methods | Search | Browse

Genome-wide meta-analysis results of all included datasets

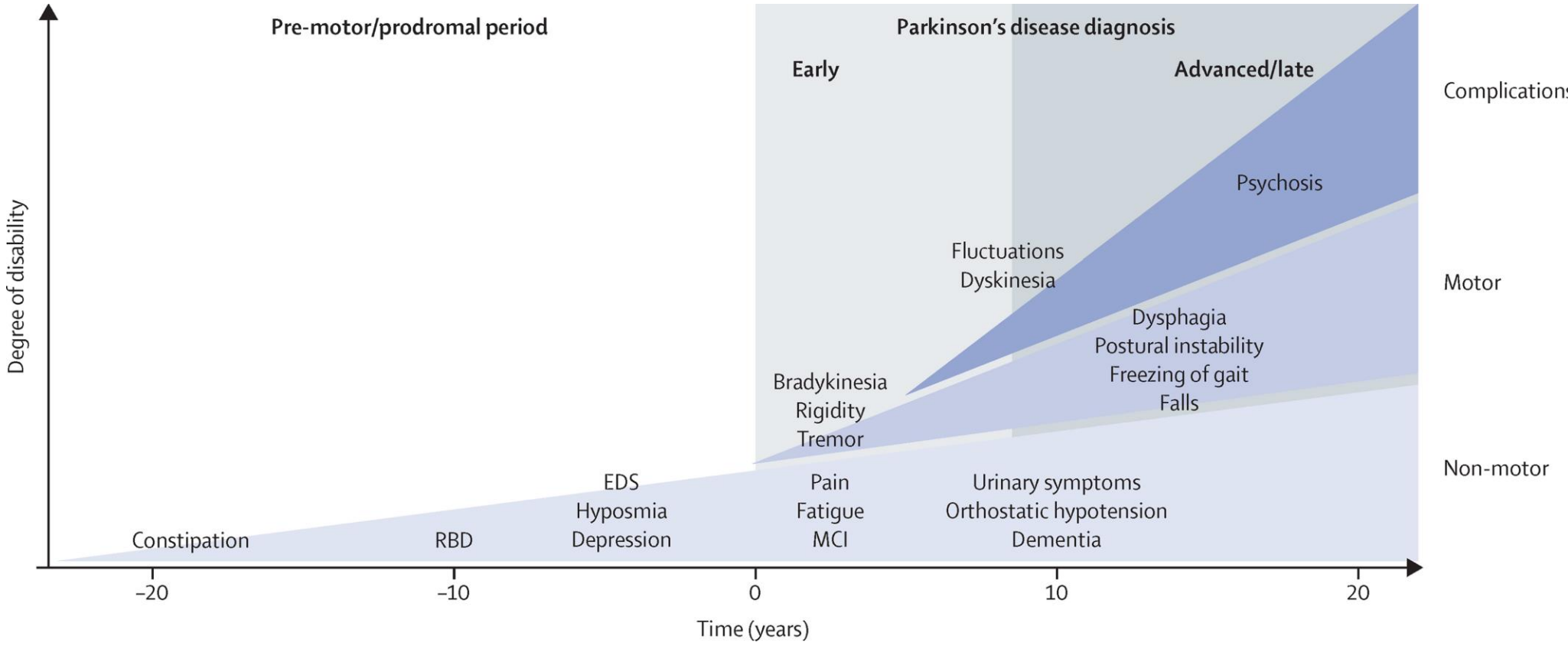


Genetic contribution to PD

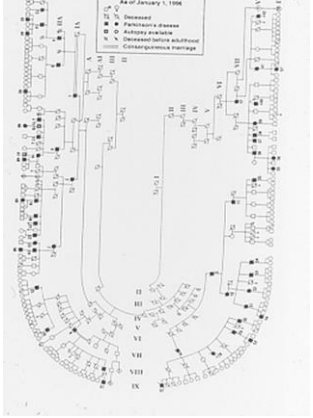
- **Case control studies**

- **relative risk of 2.3 for first degree relatives of index PD cases (community-based study)** *(Marder et al, 1996; Marder et al, 2003)*

Clinical symptoms & time course of PD progression



Kalia & Lang (2015)



Synucleinopathies

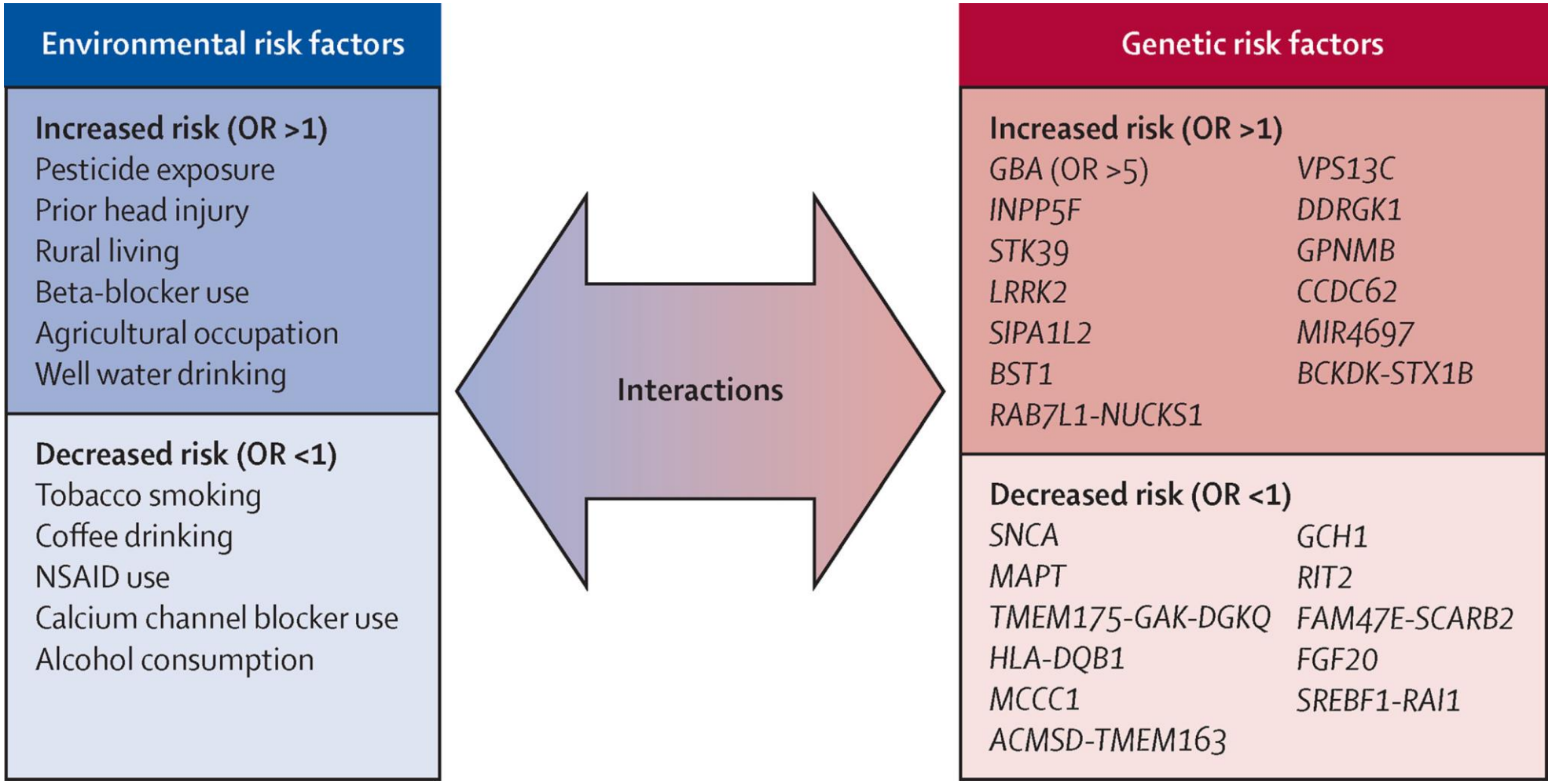
Golbe et al, 1996; Galvin et al, 2001; Popescu et al, 2005

- PD
  - Sporadic
  - Familial with alpha-syn mutations
  - Familial without alpha-syn mutations
- Dementia with Lewy Bodies
  - Pure LB dementia
  - LB variant of AD
  - Familial AD with APP/ PS-1/ PS-2 mutations
  - Down syndrome
- Multiple system atrophy
- Neurodegeneration with brain iron accumulation type 1
  - Hallervorden-Spatz syndrome
  - Neuroaxonal dystrophy
- Other disorders
  - Traumatic brain injury
  - Pick disease
  - Argyrophilic grain disease
  - ALS

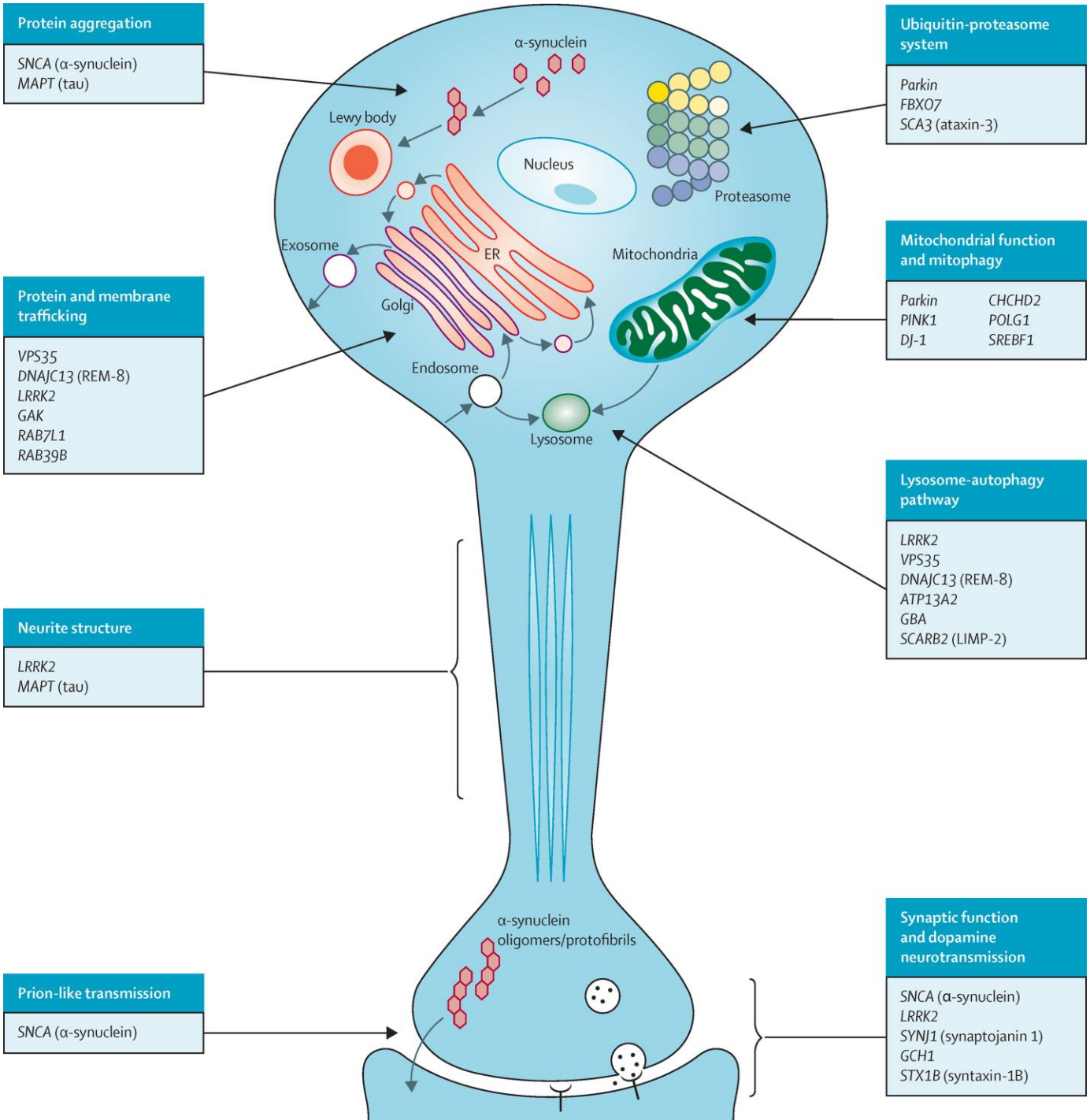
Mendelian Parkinson's Loci: one process or more?

LOCUS1	Inheritance	Onset	Protein	Path
PARK-1/4	AD	~45	Alpha-synuclein	LB
PARK-2	AR	7-60	Parkin	None
PARK-6	AR	36-60	PINK-1	one case with LB
PARK-7	AR	27-40	DJ-1	Nigral degeneration, diffuse LBs spheroids
PARK-8	AD	45-57	LRRK2	Usually LB, variable tau deposition
PARK-9 (Kufor-Rakeb sy.)	AR	Teens	ATP13A2	Absent LBs; neuronal & glial lipofuscinosis
PARK-14	AR	Teens	PLA2G6	LB, also spheroids brain iron Xs
PARK-15	AR	Teens	FBXO7	?
PARK-17	AD	50-70	VPS35	?
PARK-18				

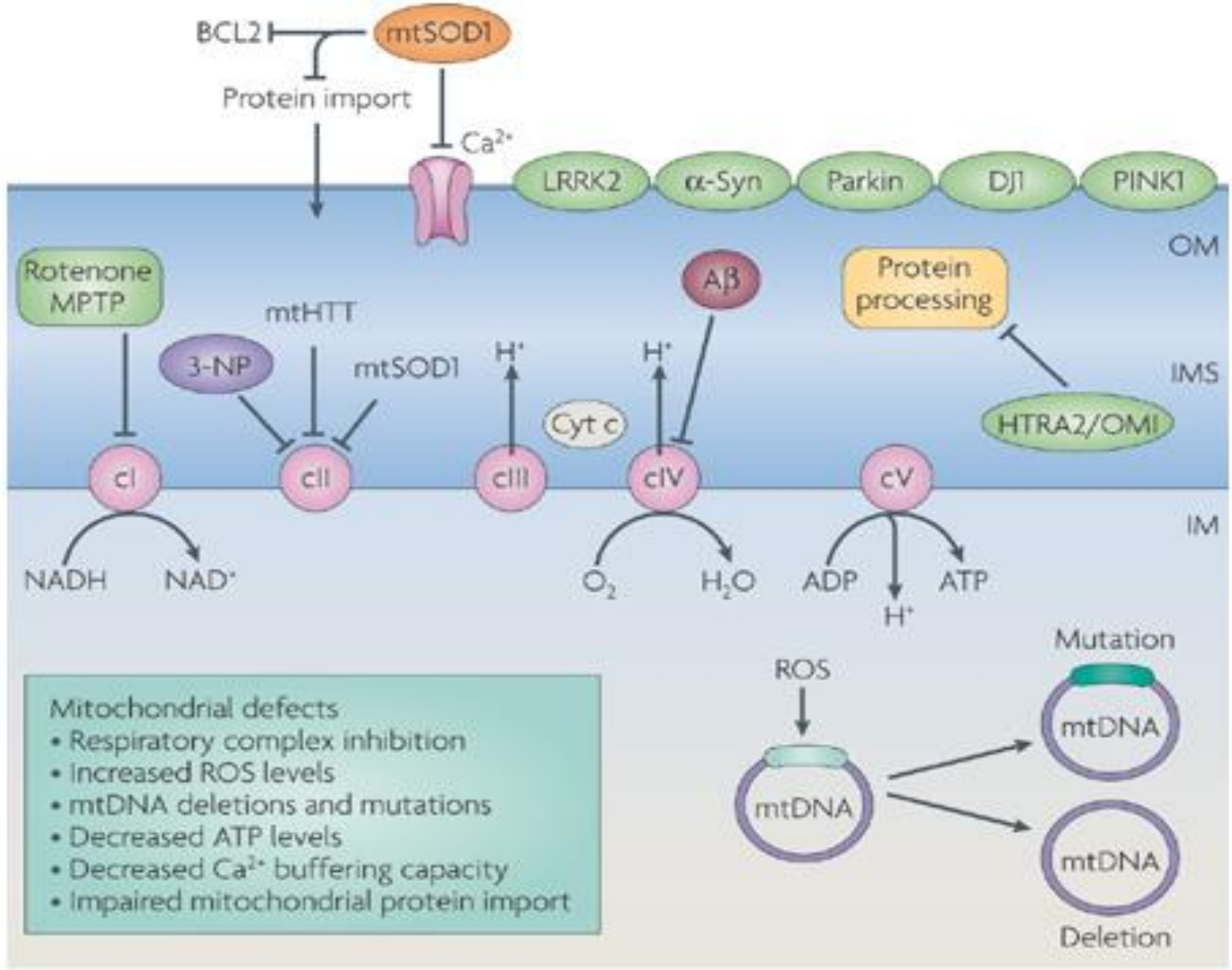
PARK-14	AR	Teens	PLA2G6	LB, also spheroids brain iron Xs
PARK-15	AR	Teens	FBXO7	?
PARK-17	AD	50-70	VPS35	?
PARK-18	AR	Late onset	EIF4G1	LBs
PARK-19	AR	Juvenile onset	DNAJC6	?
PARK-20	AR	Early onset	SYNJ1	?
PARK-21	AD	Late onset PD/PSP	DNAJC13	Brain stem or transitional LB. tauopathy
PARK-22 ?	AD	Late onset (Japanese)	CHCHD2	?
PARK-23	AR	Early onset, rapid	VPS13C	LB present



From Kalia & Lang (2015)



Cellular processes Involved in pathogenesis of PD

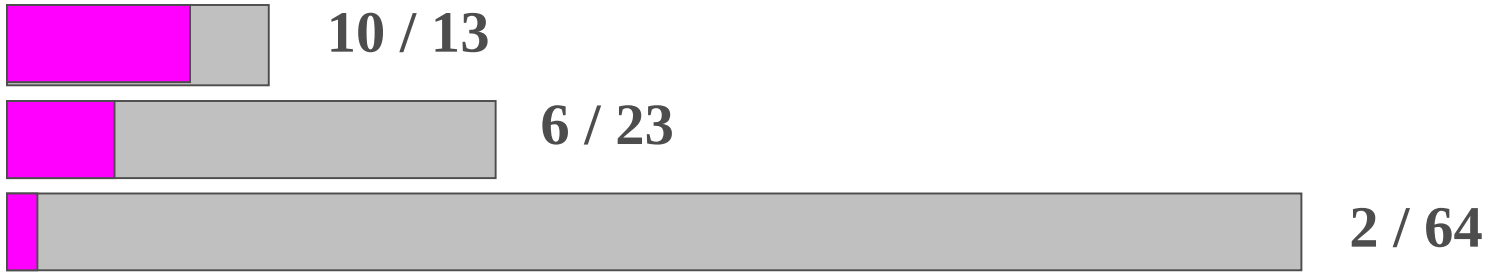

BCL2
mtSOD1
Protein import
Ca2+
LRRK2
α-Syn
Parkin
DJ1
PINK1
OM
Rotenone
MPTP
mtHTT
3-NP
mtSOD1
Aβ
Protein
processing
IMS
H+
H+
Cyt c
HTRA2/OMI
cI
cII
cIII
cIV
cV
IM
NADH
NAD+
O2
H2O
ADP
ATP
H+
Mutation
ROS
mtDNA
mtDNA
mtDNA
Deletion
Mitochondrial defects
• Respiratory complex inhibition
• Increased ROS levels
• mtDNA deletions and mutations
• Decreased ATP levels
• Decreased Ca2+ buffering capacity
• Impaired mitochondrial protein import

Parkin disease - frequencies

1998-2004 - more than 80 mutations found

Families (onset <45y): **49 %** **36 / 73**

Isolated cases: **18 %** **18 / 100**



Lücking et al., N Engl J Med 2000

THE UNIVERSITY OF BIRMINGHAM

Kilarski et 2012

- **Systematic review and UK-based study of PARK2 (parkin), PINK1, PARK7 (DJ-1) and LRRK2 in early-onset Parkinson's disease.**

3.6% of patients have AAO <45y; n=136

		Freq	Ethnicity
PARK2	parkin	8.6%	All
PARK7	DJ1	0.4%	All

Parkin disease - phenotypes

typical features:
- early-onset, mean 32 ± 11 y.rs, range 7-68
- good levodopa-response
- recessive inheritance (familial, isolated cases)
- slow progression

- l-dopa-induced fluctuations and dyskinesias
- rare cognitive or vegetative involvement
- dystonia at onset, brisk reflexes, sleep benefit

“overlap” phenotypes:
Dopa-responsive dystonia (plus mild parkinsonian signs)
Late-onset “clinically classical” Parkinson’s disease

protein quality control system and PD

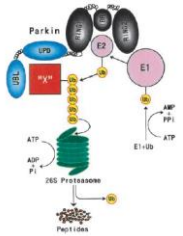
α-synuclein

synphilin-1

PAEL receptor

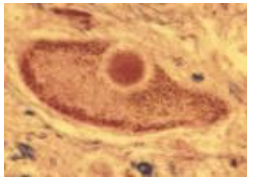
Parkin

ubiquitylation



proteasomal degradation

aggresome formation



protein misfolding

oxidative stress

DJ-1

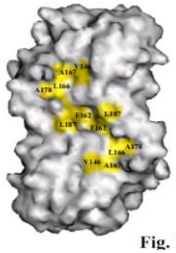


Fig. 1

chaperones
refolding
stress response

THE UNIVERSITY OF BIRMINGHAM

Genetic loci implicated in PD

Locus	Chromosomal location	Inheritance	Protein	Putative function
PARK1	4q21	AD	α synuclein	?
PARK2	6q25.2-27	AR	Parkin	E3 ubiquitin ligase
PARK3	2p13	AD	?	
PARK4	4q21	AD	α synuclein	?
PARK5	4p14	AD	UCH-L1	Ubiquitin C-terminal ligase
PARK6	1p36	AR	PINK1	Mitochondrial protein kinase
PARK7	1p36	AR	DJ-1	Chaperone, oxidative stress response
PARK8	12p11.2-13.1	AD	LRRK2	phosphorylation
PARK9	1p36	?AR	?	
GBA	1q21	Susceptilitity factor	Glucocerebrosidase	Glucocerebrosidase hydrolase

Neuron, Vol. 44, 595–600, November 18, 2004, Copyright ©2004 by Cell Press

Cloning of the Gene Containing Mutations that Cause *PARK8*-Linked Parkinson's Disease

Coro Paisán-Ruíz,[1,11] Shushant Jain,[2,3,11] E. Whitney Evans,[4] William P. Gilks,[3] Javier Simón,[1] Marcel van der Brug,[5] Adolfo López de Munain,[6,7] Silvia Aparicio,[1] Angel Martínez Gil,[8] Naheed Khan,[3] Janel Johnson,[4] Javier Ruiz Martinez,[9] David Nicholl,[10] Itxaso Marti Carrera,[7] Amets Saénz Peña,[6] Rohan de Silva,[3] Andrew Lees,[3] José Félix Martí-Massó,[7] Jordi Pérez-Tur,[1,*] Nick W. Wood,[2,*] and Andrew B. Singleton[4,*]

Leucine-rich repeat kinase 2 (*LRRK2*)

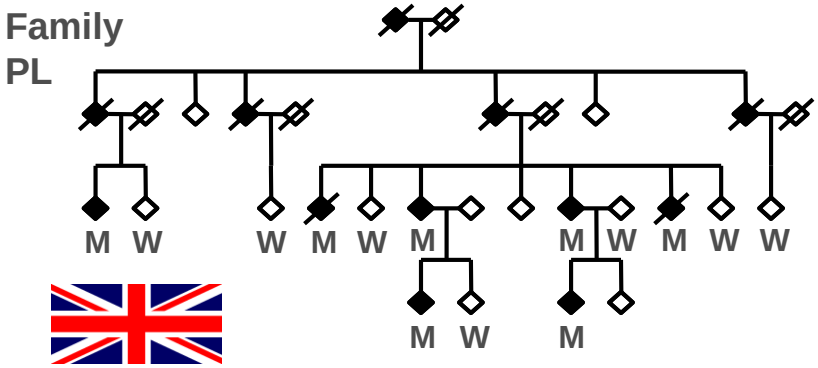
Dardarin Protein

Neuron, Vol. 44, 601–607, November 18, 2004, Copyright ©2004 by Cell Press

Mutations in *LRRK2* Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology

Alexander Zimprich,[1,2,11] Saskia Biskup,[3,11] Petra Leitner,[1] Peter Lichtner,[3] Matthew Farrer,[4] Sarah Lincoln,[4] Jennifer Kachergus,[4] Mary Hulihan,[4] Ryan J. Uitti,[5] Donald B. Calne,[6] A. Jon Stoessl,[6] Ronald F. Pfeiffer,[7] Nadja Patenge,[1] Iria Carballo Carbajal,[1] Peter Vieregge,[8] Friedrich Asmus,[1] Bertram Müller-Myhsok,[9] Dennis W. Dickson,[4] Thomas Meitinger,[3,10,*] Tim M. Strom,[3,10] Zbigniew K. Wszolek,[5,*] and Thomas Gasser[1,*]

PARK-8 PD Funayama et al, 2002- Sagamihara kindred



Age at exam 67y
Onset 42y

Y1699C mutation in exon 35

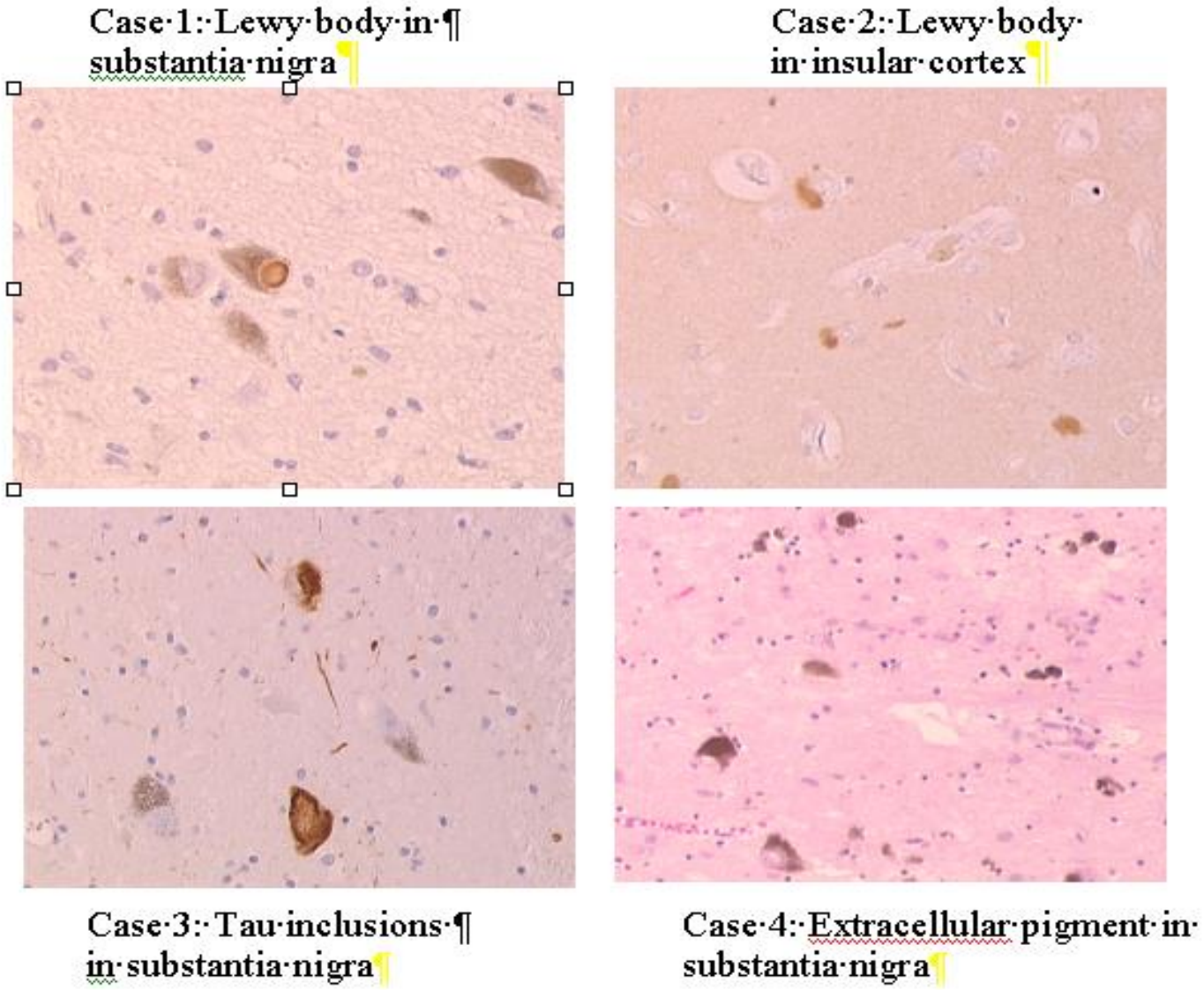
Nicholl et al, Brain 2002;125:44; Khan N et al, 2005

THE UNIVERSITY OF BIRMINGHAM

PARK8

- *LRRK2-*
  - 51 exons
- Gly2019Ser responsible for a significant portion of dominant disease (5-6% of familial cases & 1-2% of sporadic cases

- Mutations contribute to apparently sporadic disease
- LRRK2 protein contains LRR, WD40, kinase and RAS/RAB domain
- Function- mixed lineage kinase activity & autophosphorylation activity



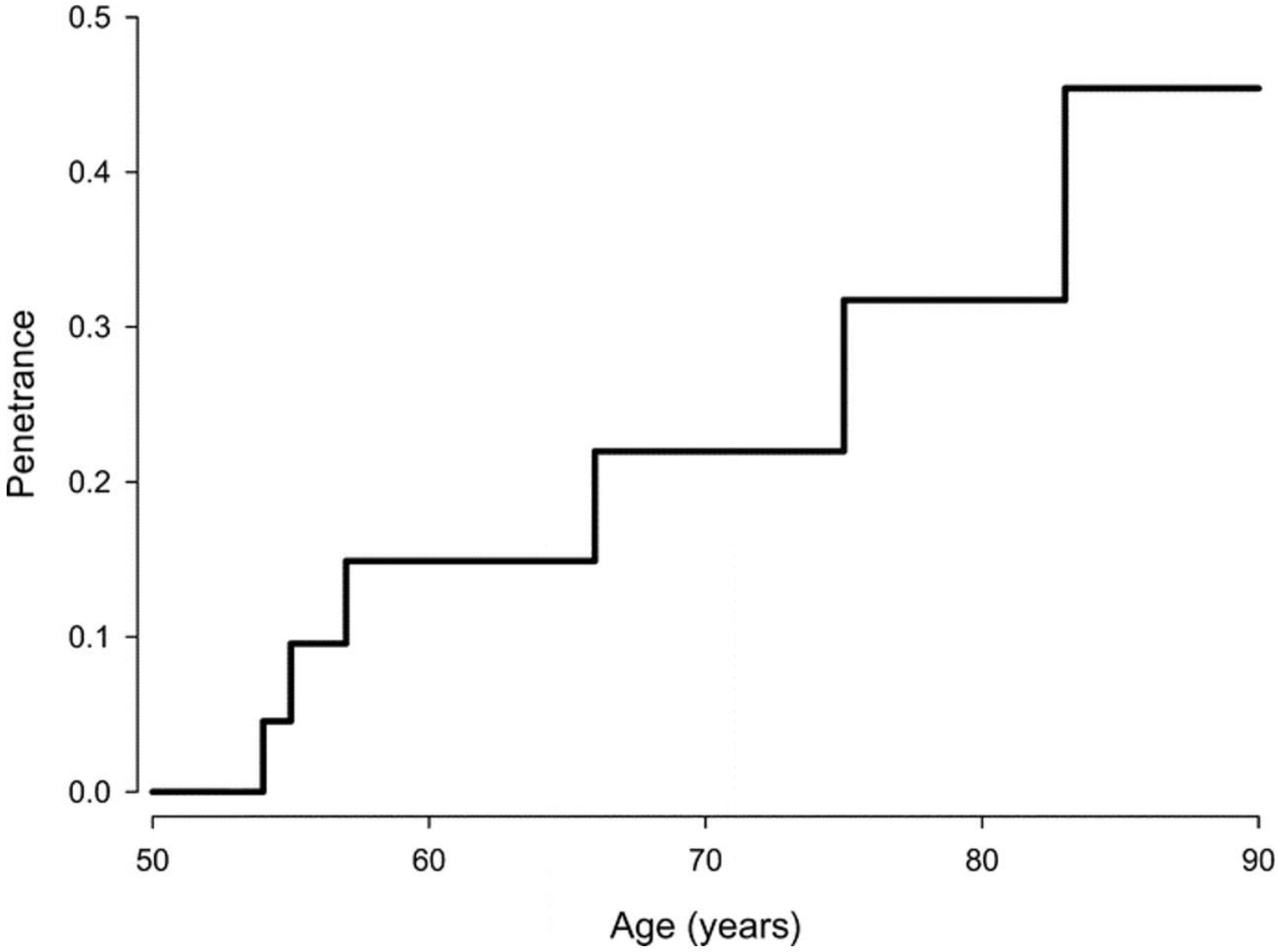
PARK8 Neuropathology

Wszolek Z et al, Neurology 2004; 62:1619;
Zimprich et al, 2004; Rajput et al, Neurology, 2006;
Ross et al, 2006
Giasson et al, 2006

LRRK2- penetrance

- Age related penetrance
  - 17% at 50 years
  - 85% at 70 years
  - (Karchergus et al, 2005)
  - Varies according to geographic origin
    - 30% Europeans
    - 10% North Africans
  - Disease progression- slower
    - JAMA Neurol. 2018 Jan 8.
  - 85 y old G2019S carrier with no signs of PD (Kay et al, 2005)

Figure. Kaplan-Meier analysis of the cumulative incidence of Parkinson disease among 36 subjects carrying the LRRK2-G2019S mutation.



Goldwurm S et al. Neurology 2007;68:1141-1143

LRRK2 G2019S is common & dependent on ethnicity

	Sporadic	Familial	Control
N African Arabs	39%	36%	<1%
Ashkenazi Jews	10%	28%	<1%
UK British	1%	2%	0%
Welsh	0.3%	1.5%	NA

Healy D et al. Lancet Neurol 2008

Summary

- 23 different genetic loci and 16 genes (alpha-synuclein, parkin, DJ-1, PINK1 and UCHL1, ATP13A2 & LRRK2) in last 20 years
- Ubiquination, protein aggregation, autophagy & formation of Lewy bodies appears central to PD pathogenesis

LRRK2 in clinical practice?

- Role of G2019S screening
  - Genetic counselling (cf Huntington's)
  - Reduced penetrance
  - Interaction with other proteins, eg parkin
  - role for kinase inhibitors in neuroprotection of PD
    - West A. Exp Neurol. 2017 Dec;

Google founder finds out he has Parkinson's risk after taking wife's genetic test

Last updated at 3:44 PM on 19th September 2008

Comments (0) | Add to My Stories

Google's co-founder Sergey Brin has discovered he has an increased risk of developing Parkinson's disease, after taking a genetic test by a company founded by his wife.

Writing on his personal blog, the 35-year-old revealed both he and his mother carry the G2019S mutation of the LRRK2 gene, which is linked to a rare hereditary form of the degenerative brain disorder.

His mother, who worked with computers for NASA, thought she has repetitive strain injury after she suffered pain in her hands. She has since been diagnosed with the disease.

FEMAIL TODAY

Katie Price shows Peter - and a packed beach - what he's missing as she shoots raunchy calendar

Model thrust out porn star

Are neurologists being too fussy over the diagnostic issues?

Web-Based Genome-Wide Association Study Identifies Two Novel Loci and a Substantial Genetic Component for Parkinson's Disease

Chuong B. Do[1*], Joyce Y. Tung[1], Elizabeth Dorfman[1], Amy K. Kiefer[1], Emily M. Drabant[1], Uta Francke[1], Joanna L. Mountain[1], Samuel M. Goldman[2], Caroline M. Tanner[2], J. William Langston[2], Anne Wojcicki[1], Nicholas Eriksson[1*]

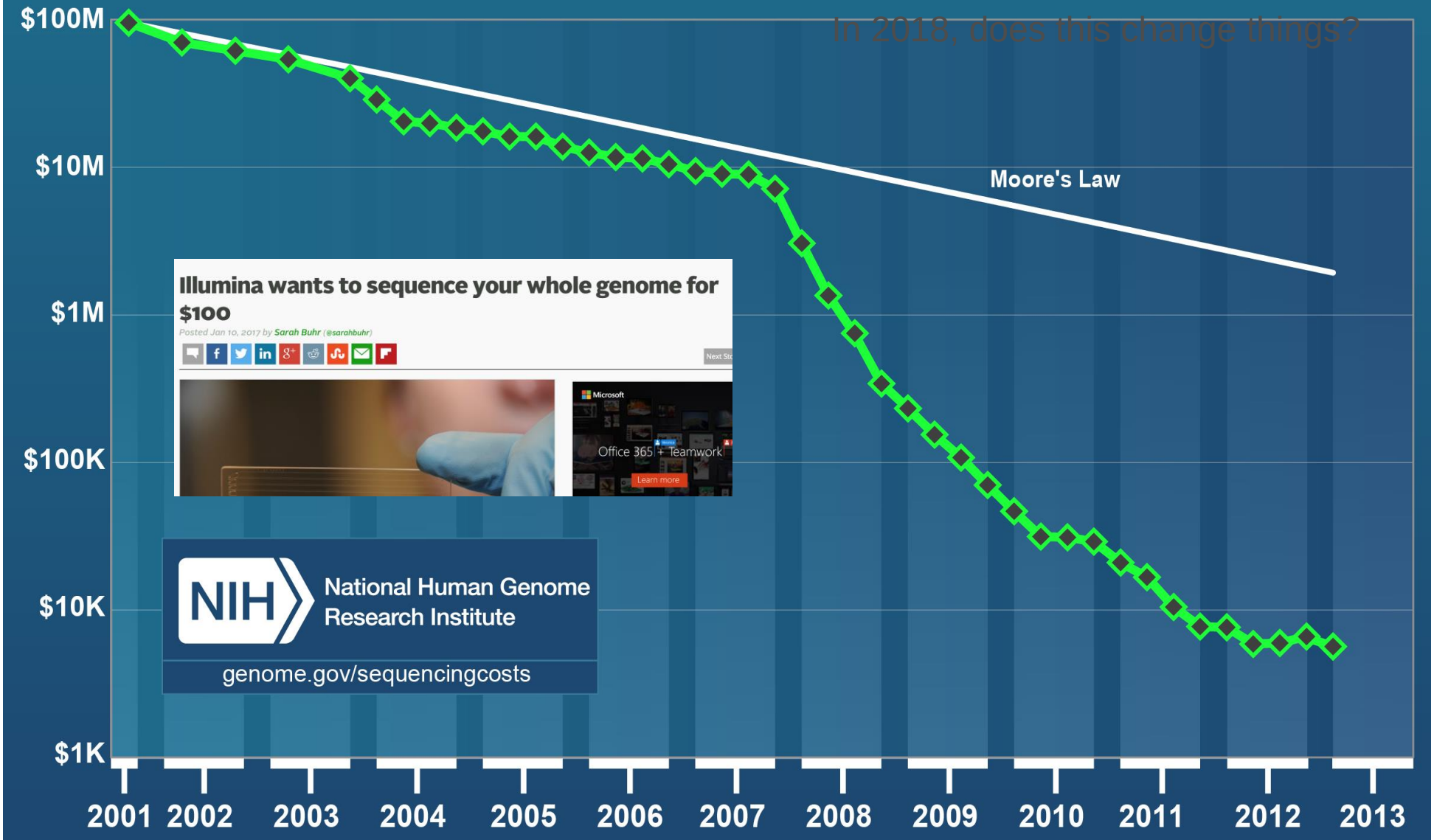
1 23andMe, Mountain View, California, United States of America, **2** Parkinson's Institute, Sunnyvale, California, United States of America

Abstract

My requests for DNA tests- 2002-2012 (Appleton el JNNP (2013)

- 137 requests in 111 patients (45 (16-81)y)
  - 21.9% DNA banking
  - 78.1% for tests (82)
    - DRD (GTP Cyclohydrolase)(14)
    - SCA (11)
    - Parkin (8)
    - LRRK2 (8)
    - Friederich's (7)
    - Wilson's (6)
    - Lebers (6)
    - 20.6% showed an abnormality

Cost per Genome



Presymptomatic testing for late-onset genetic disorders (adapted from Harper, 1997)

- **Huntington's disease**
- Serious & ultimately fatal
- Currently not treatable
- Onset most often in middle life
- Autosomal dominant
- Relatively frequent
- Specific genetic testing feasible
- Testing introduced with careful preparation
- Accurate documentation of testing experience
- Close co-operation & co-ordination of protocols worldwide

- **Parkinson's disease**

- Usually older age
- Most idiopathic; AD; AR
- Mendelian families rare
- Genetics complex- known genes large!

- OTHER problems:
  - Penetrance
  - Phenocopies
  - Many different genetic loci with an identical phenotype

Genetic testing for PD?

- Do we know the causative gene?
- Do we know the frequency of disease causing mutations?
- Are we able to prioritise patients based on suggestive clinical features?
- What is the sensitivity/specificity of the genetic test?
- How reliable is the lab performing the tests?
- Will genetic testing alter patient management?
- Could variations in these genes affect sporadic PD?

J Genet Couns. 2017 Sep 30.

- Survey of subjects- **Patients' Opinions on Genetic Counseling on the Increased Risk of Parkinson Disease among Gaucher Disease Carriers.**
-
- 86.7% believed that patients should be informed about the increased risk of PD prior to having GD carrier screening

Referral to neurology from genetics

- 35y old Pakistani male referred as child with learning difficulties
  - Found to have partial deletion of chr 6
  - “Is he at risk of developing Parkinson’s disease?”

Referral to Gp from paediatric neurology

- “Can you send a DNA for PD NGS panel on this 17y old man with tremor?”

- “I’ll think I’ll ask a neurologist”

- Define the phenotype
- Take a Family History
- WHY TEST????

56 y old female with idiopathic torsion dystonia

- Onset aged 29y
- 24h urine copper- normal
- MRI head- normal

- NGS dystonia panel heterozygous variant in ATP7B gene
- What does this mean?

Table 2. Benefits, Misconceptions, and Limitations of the Genomewide Association Study.

Benefits
Does not require an initial hypothesis
Uses digital and additive data that can be mined and augmented without data degradation
Encourages the formation of collaborative consortia, which tend to continue their collaboration for subsequent analyses
Rules out specific genetic associations (e.g., by showing that no common alleles, other than *APOE*, are associated with Alzheimer's disease with a relative risk of more than 2)
Provides data on the ancestry of each subject, which assists in matching case subjects with control subjects
Provides data on both sequence and copy-number variations
Misconceptions
Thought to provide data on all genetic variability associated with disease, when in reality only common alleles with large effects are identified
Thought to screen out alleles with a small effect size, when in reality such findings may still be very useful in determining pathogenic biochemical pathways, even though low-risk alleles may be of little predictive value
Limitations
Requires samples from a large number of case subjects and control subjects and therefore can be challenging to organize
Finds loci, not genes, which can complicate the identification of pathogenic changes on an associated haplotype
Detects only alleles that are common (>5%) in a population
Requires replication in a similarly large number of samples

GWAS and Parkinson's disease- Nature Genetics- Dec 2009


Simon-Sanchez et al GWAS reveals genetic risk underlying PD 2009.pdf - Adobe Reader

File Edit View Document Tools Window Help

1308 (1 of 7) 105% Find

LETTERS

nature genetics

Genome-wide association study revea
underlying Parkinson's disease

Javier Simón-Sánchez[1,2,22], Claudia Schulte[3,22], Jose M Bras[1,4,22], Manu Sha
Coro Paisan-Ruiz[5], Peter Lichtner[6], Sonja W Scholz[1,5], Dena G Hernandez
Christine Klein[7], Alison Goate[8], Joel Perlmutter[8], Michael Bonin[9], Michae
Christian Gieger[10], Henry Houlden[5], Michael Steffens[11], Michael S Okun
Kelly D Foote[12], Hubert H Fernandez[12], Bryan J Traynor[1], Stefan Schreibe
Katrina Gwinn[14], Marcel van der Brug[1,15], Grisel Lopez[16], Stephen J Chan
Yikyung Park[17], Albert Hollenbeck[18], Jianjun Gao[19], Xuemei Huang[20], Ni
Günther Deuschl[21], Honglei Chen[19], Olaf Riess[9], John A Hardy[5], Andrew

We performed a genome-wide association study (GWAS) in 1,713 individuals of European ancestry with Parkinson's disease (PD) and 3,978 controls. After replication in 3,361 cases and 4,573 controls, we observed two strong association signals, one in the gene encoding α-synuclein (*SNCA*; rs2736990, OR = 1.23, $P = 2.24 \times 10^{-16}$) and another at the *MAPT* locus

new era in the inv
So far, GWAS ha
because previous
expected in these
The present stud
of the cohorts are

merica, Inc. All rights reserved.

Satake et al GWAS identifies common variants at 4 loci as genetic risk factors for PD 2009.pdf - Adobe Reader

File Edit View Document Tools Window Help

1303 (1 of 6) 105% Find

LETTE

nature genetics

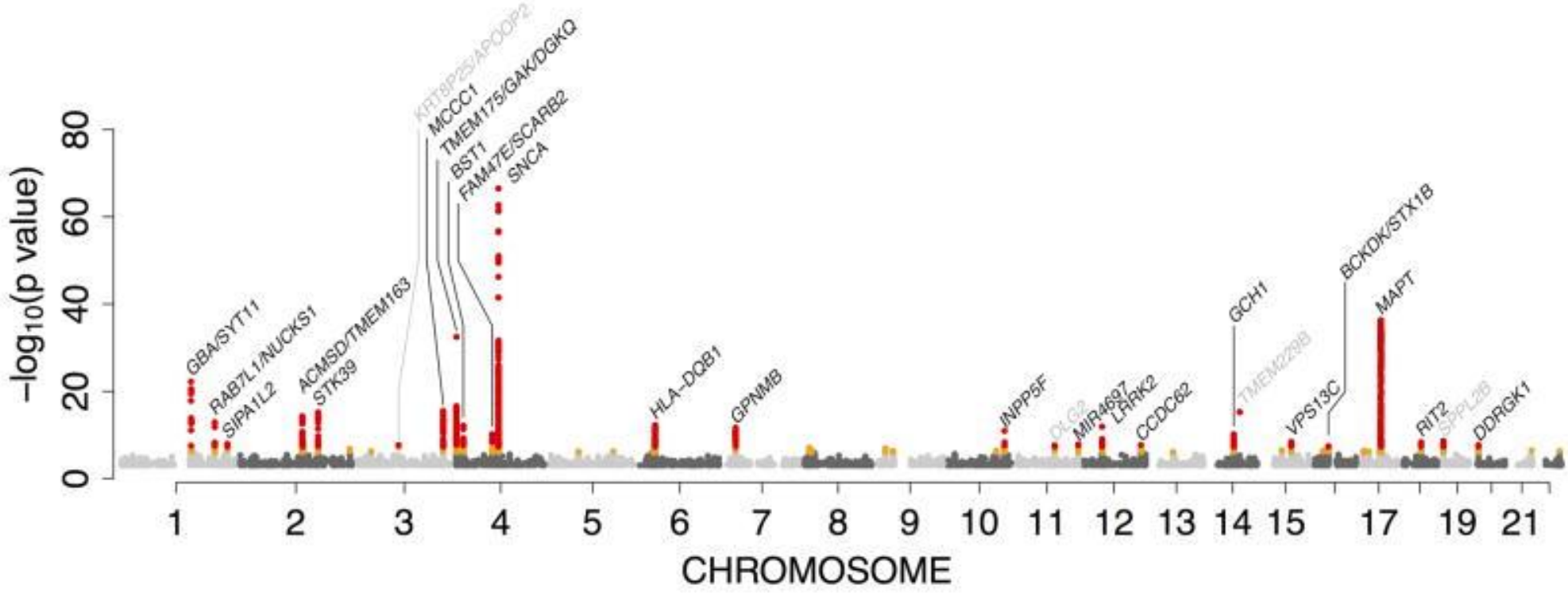
Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

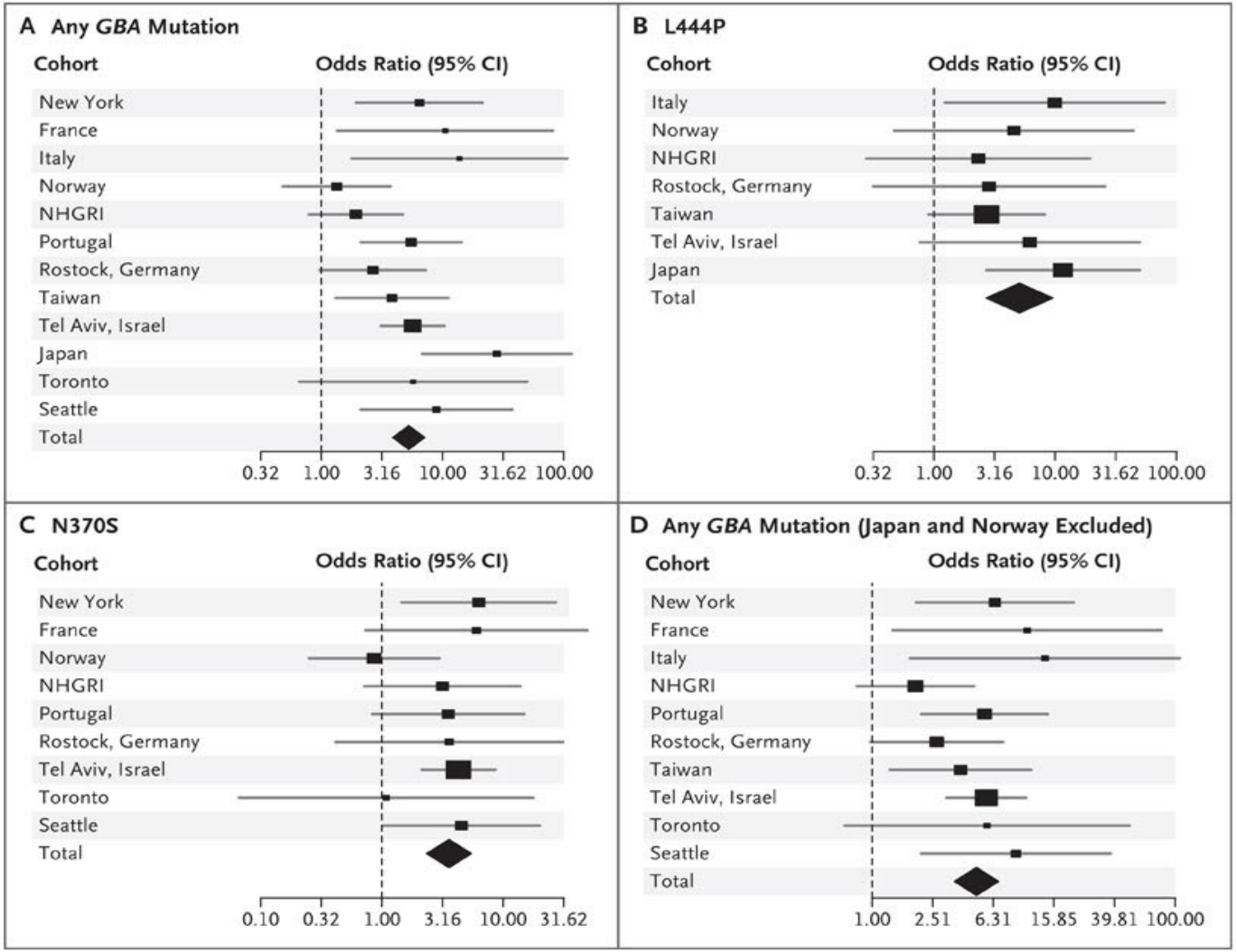
Wataru Satake[1–3], Yuko Nakabayashi[1,2], Ikuko Mizuta[1,2], Yushi Hirota[1,2], Chiyomi Ito[1,2], Michiaki Kubo[4], Takahisa Kawaguchi[4], Tatsuhiko Tsunoda[4], Masahiko Watanabe[5], Atsushi Takeda[6], Hiroyuki Tomiyama[7], Kenji Nakashima[8], Kazuko Hasegawa[9], Fumiya Obata[10], Takeo Yoshikawa[11], Hideshi Kawakami[12], Saburo Sak
Mitsutoshi Yamamoto[13], Nobutaka Hattori[7], Miho Murata[14], Yusuke Nakamura[4,15] & Tatsushi Toda[1,2]

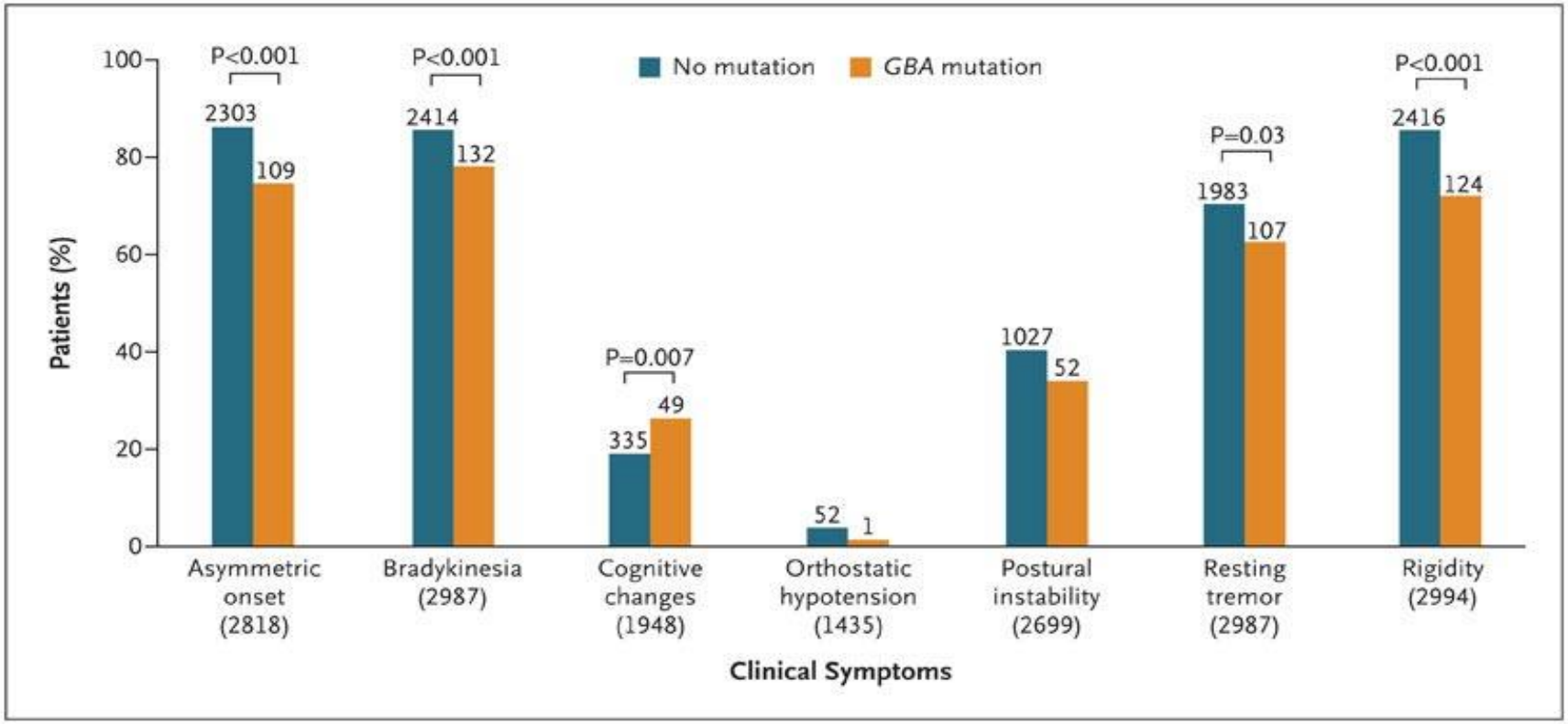
To identify susceptibility variants for Parkinson's disease (PD), we performed a genome-wide association study (GWAS) and two replication studies in a total of 2,011 cases and 18,381 controls from Japan. We identified a new susceptibility locus on 1q32 ($P = 1.52 \times 10^{-12}$) and designated this as *PARK16*, and we also identified *BST1* on 4p15 as a second new risk

forms[5,6]. However, mendelian forms of parkinsonism a
compared to the far more common typical PD, a complex d
caused by multiple genetic and environmental factors[7]. Asso
studies have evaluated variants in many candidate genes for P
only a few, such as common variants of *SNCA*[8–10] and rare
tions of *GBA*[11], have been identified as PD-susceptibility gen

Inc. All rights reserved.


−log10(p value)
0
20
40
60
80
GBA/SYT11
RAB7L1/NUCKS1
SIPA1L2
ACMSD/TMEM163
STK39
KRT8P25/APOOP2
MCCC1
TMEM175/GAK/DGKQ
BST1
FAM47E/SCARB2
SNCA
HLA-DQB1
GPNMB
INPP5F
OLG2
MIR4697
LRRK2
CCDC62
GCH1
TMEM229B
VPS13C
BCKDK/STX1B
MAPT
RIT2
SPPL2B
DDRGK1
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
17
19
21
CHROMOSOME





The NEW ENGLAND JOURNAL of MEDICINE

GBA mutation assoc with lower glucocerebrosidase activity (Alcalay RN et al 2015)

GBA & Parkinsonism

- Mutations in *GBA1* can be found in 4% to 7% of PD cases
- reduced activity of β-glucocerebrosidase appears to be a common feature of most (and perhaps nearly all) cases of PD, even when no mutation in the gene can be detected

Role of the lysosome

- **Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease.**
- confirmed associations at the GBA and SMPD1 loci
- CTSD, SLC17A5 & ASAH1 as candidate Parkinson's disease susceptibility genes.

- Robak et al. Brain. 2017 Dec 1

Where next with PD genetics & technology?

-Should we start thinking about pharmacogenetics more seriously?

-Eg Tolcapone & liver failure

-Pharmacogenomics J. 2002;2(5):327-34

-SNPs in UDP-glucuronosyl transferase 1A gene complex

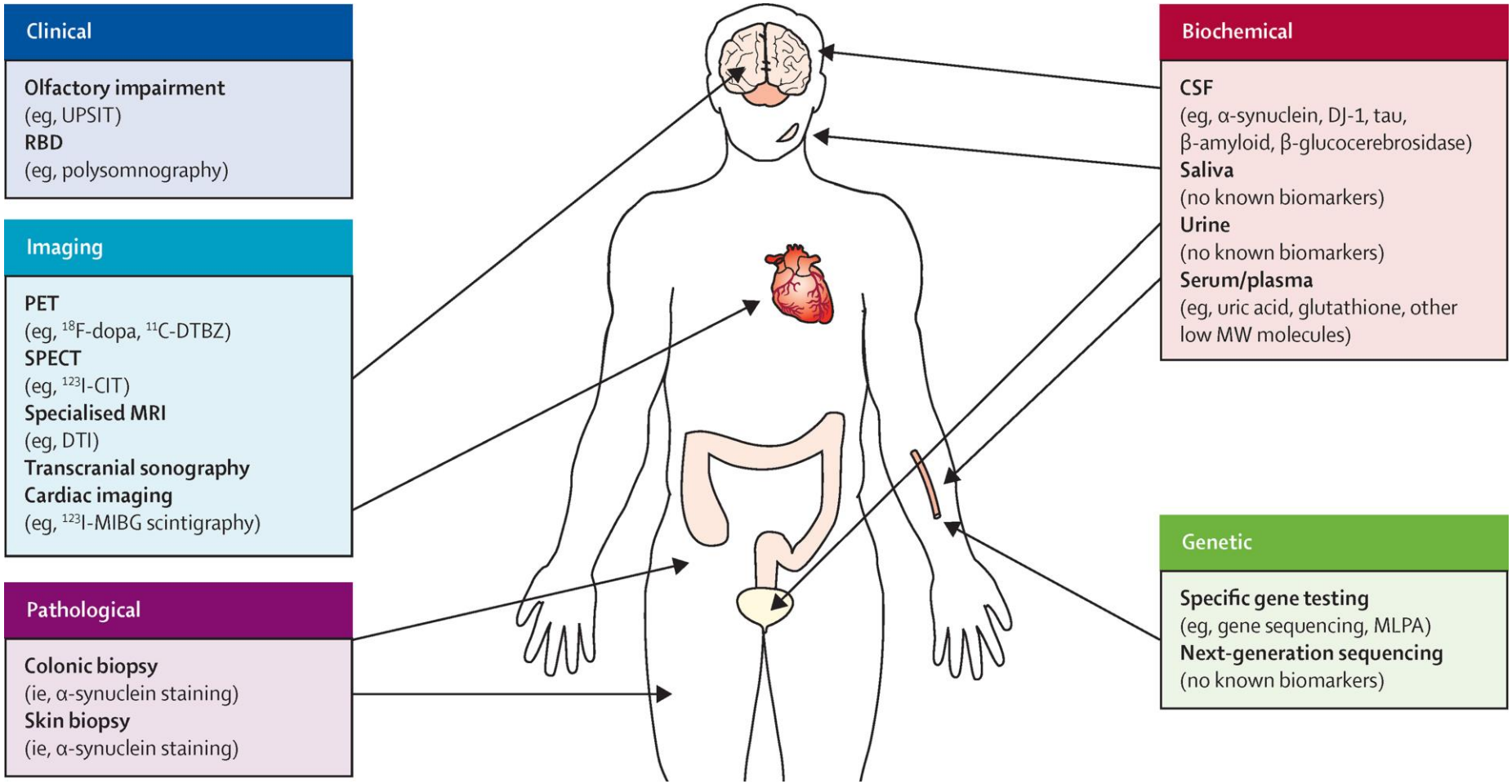
Dopamine D2 receptor gene variants and response to rasagiline in early Parkinson's disease:
a pharmacogenetic study. (Masellis et al, Brain 2016)

MIT Technology Review 50 SMARTEST COMPANIES

The UK 100,000 Genomes Project

February 2015

www.genomicsengland.co.uk



Potential biomarkers for diagnosis of PD (from Kalia & Lang (2015))

In summary

- Do NOT underestimate the importance of clinical observation….from James Parkinson, to GBA
- Take a Family History
- Selective investigation! (onset <50y; good FH; atypical features)