The Aetiology & pathogenesis of Parkinson’s disease

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@bhammodis
Structure of this talk

- **Background**
  - Genetics of Parkinson’s disease
    - Focusing on recent developments
  - Clinical relevance
    - What do I tell my patients?
    - Investigations
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 NexLera 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 deletions/duplications/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 (L1: all 7 coding exons and a region 8' to exon 1), ATP13A2 coding exons 2 and 9, the AIB130Pro 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 HGV: (Human Genome Variation Society) guidelines: www.genetests.org/; www.ncbi.nlm.nih.gov


The Neurogenetics Laboratory is UKAS accredited medical laboratory No.9240. 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.

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.
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)
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/](http://www.pdgene.org/)
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?

<table>
<thead>
<tr>
<th>LOCUS1</th>
<th>Inheritance</th>
<th>Onset</th>
<th>Protein</th>
<th>Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK-1/4</td>
<td>AD</td>
<td>~45</td>
<td>Alpha-synuclein</td>
<td>LB</td>
</tr>
<tr>
<td>PARK-2</td>
<td>AR</td>
<td>7-60</td>
<td>Parkin</td>
<td>None</td>
</tr>
<tr>
<td>PARK-6</td>
<td>AR</td>
<td>36-60</td>
<td>PINK-1</td>
<td>one case with LB</td>
</tr>
<tr>
<td>PARK-7</td>
<td>AR</td>
<td>27-40</td>
<td>DJ-1</td>
<td>Nigral degeneration, diffuse LBs spheroids</td>
</tr>
<tr>
<td>PARK-8</td>
<td>AD</td>
<td>45-57</td>
<td>LRRK2</td>
<td>Usually LB, variable tau deposition</td>
</tr>
<tr>
<td>PARK-9</td>
<td>AR (Kufor-Rakeb sy.)</td>
<td>Teens</td>
<td>ATP13A2</td>
<td>Absent LBs; neuronal &amp; glial lipofuscinosisis</td>
</tr>
<tr>
<td>PARK-14</td>
<td>AR</td>
<td>Teens</td>
<td>PLA2G6</td>
<td>LB, also spheroids brain iron Xs</td>
</tr>
<tr>
<td>PARK-15</td>
<td>AR</td>
<td>Teens</td>
<td>FBXO7</td>
<td>?</td>
</tr>
<tr>
<td>PARK-17</td>
<td>AR</td>
<td>50-70</td>
<td>VPS35</td>
<td>?</td>
</tr>
<tr>
<td>PARK-18</td>
<td>AD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK-14</td>
<td>AR</td>
<td>Teens</td>
<td>PLA2G6</td>
<td>LB, also spheroids brain iron Xs</td>
</tr>
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</tr>
<tr>
<td>PARK-15</td>
<td>AR</td>
<td>Teens</td>
<td>FBXO7</td>
<td>?</td>
</tr>
<tr>
<td>PARK-17</td>
<td>AD</td>
<td>50-70</td>
<td>VPS35</td>
<td>?</td>
</tr>
<tr>
<td>PARK-18</td>
<td>AR</td>
<td>Late onset</td>
<td>EIF4G1</td>
<td>LBs</td>
</tr>
<tr>
<td>PARK-19</td>
<td>AR</td>
<td>Juvenile onset</td>
<td>DNAJC6</td>
<td>?</td>
</tr>
<tr>
<td>PARK-20</td>
<td>AR</td>
<td>Early onset</td>
<td>SYNJ1</td>
<td>?</td>
</tr>
<tr>
<td>PARK-21</td>
<td>AD</td>
<td>Late onset PD/PSP</td>
<td>DNAJC13</td>
<td>Brain stem or transitional LB. tauopathy</td>
</tr>
<tr>
<td>PARK-22 ?</td>
<td>AD</td>
<td>Late onset (Japanese)</td>
<td>CHCHD2</td>
<td>?</td>
</tr>
<tr>
<td>PARK-23</td>
<td>AR</td>
<td>Early onset, rapid</td>
<td>VPS13C</td>
<td>LB present</td>
</tr>
</tbody>
</table>
From Kalia & Lang (2015)

Environmental risk factors

- Increased risk (OR >1)
  - Pesticide exposure
  - Prior head injury
  - Rural living
  - Beta-blocker use
  - Agricultural occupation
  - Well water drinking

- Decreased risk (OR <1)
  - Tobacco smoking
  - Coffee drinking
  - NSAID use
  - Calcium channel blocker use
  - Alcohol consumption

Genetic risk factors

- Increased risk (OR >1)
  - GBA (OR >5)
  - INPP5F
  - STK39
  - LRRK2
  - SIPA1L2
  - BST1
  - RAB7L1-NUCKS1
  - VPS13C
  - DDRGK1
  - GPNMB
  - CCDC62
  - MIR4697
  - BCKD-K-STX1B

- Decreased risk (OR <1)
  - SNCA
  - MAPT
  - TMEM175-GAK-DGKQ
  - HLA-DQB1
  - MCCC1
  - ACMSD-TMEM163
  - GCH1
  - RIT2
  - FAM47E-SCARB2
  - FGF20
  - SREBF1-RAI1
Cellular processes involved in pathogenesis of PD

Protein aggregation
- SNCA (α-synuclein)
- MAPT (tau)

Ubiquitin-proteasome system
- Parkin
- FBXO7
- SCA3 (ataxin-3)

Protein and membrane trafficking
- VPS35
- DNAJC13 (REM-8)
- LRRK2
- GAK
- RAB7L1
- RAB39B

Mitochondrial function and mitophagy
- Parkin
- CHCHD2
- PINK1
- POLG1
- DJ-1
- SREBF1

Neurite structure
- LRRK2
- MAPT (tau)

lysosome-autophagy pathway
- LRRK2
- VPS35
- DNAJC13 (REM-8)
- ATP13A2
- GBA
- SCARB2 (LIMP-2)

Prion-like transmission
- SNCA (α-synuclein)

Synaptic function and dopamine neurotransmission
- SNCA (α-synuclein)
- LRRK2
- SYNJ1 (synaptoplakin 1)
- GCH1
- STX1B (syntaxin-1B)
Mitochondrial defects:
- Respiratory complex inhibition
- Increased ROS levels
- mtDNA deletions and mutations
- Decreased ATP levels
- Decreased Ca^{2+} buffering capacity
- Impaired mitochondrial protein import

Nature Reviews | Neuroscience
## Parkin disease - frequencies

1998-2004 - more than 80 mutations found

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families (onset &lt;45y):</td>
<td>49 %</td>
<td>36 / 73</td>
</tr>
<tr>
<td>Isolated cases:</td>
<td>18 %</td>
<td>18 / 100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Onset Range</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset ≤ 20</td>
<td>10 / 13</td>
</tr>
<tr>
<td>Onset 21-30</td>
<td>6 / 23</td>
</tr>
<tr>
<td>Onset 31-45</td>
<td>2 / 64</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Frequency</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK2</td>
<td>parkin</td>
<td>8.6%</td>
<td>All</td>
</tr>
<tr>
<td>PARK7</td>
<td>DJ1</td>
<td>0.4%</td>
<td>All</td>
</tr>
</tbody>
</table>
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
chaperones refolding
stress response

Fig. 1
<table>
<thead>
<tr>
<th>Locus</th>
<th>Chromosomal location</th>
<th>Inheritance</th>
<th>Protein</th>
<th>Putative function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1</td>
<td>4q21</td>
<td>AD</td>
<td>α synuclein</td>
<td>?</td>
</tr>
<tr>
<td>PARK2</td>
<td>6q25.2-27</td>
<td>AR</td>
<td>Parkin</td>
<td>E3 ubiquitin ligase</td>
</tr>
<tr>
<td>PARK3</td>
<td>2p13</td>
<td>AD</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>PARK4</td>
<td>4q21</td>
<td>AD</td>
<td>α synuclein</td>
<td>?</td>
</tr>
<tr>
<td>PARK5</td>
<td>4p14</td>
<td>AD</td>
<td>UCH-L1</td>
<td>Ubiquitin C-terminal ligase</td>
</tr>
<tr>
<td>PARK6</td>
<td>1p36</td>
<td>AR</td>
<td>PINK1</td>
<td>Mitochondrial protein kinase</td>
</tr>
<tr>
<td>PARK7</td>
<td>1p36</td>
<td>AR</td>
<td>DJ-1</td>
<td>Chaperone, oxidative stress response</td>
</tr>
<tr>
<td>PARK8</td>
<td>12p11.2-13.1</td>
<td>AD</td>
<td>LRRK2</td>
<td>phosphorylation</td>
</tr>
<tr>
<td>PARK9</td>
<td>1p36</td>
<td>?AR</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>GBA</td>
<td>1q21</td>
<td>Susceptibility factor</td>
<td>Glucocerebrosidase</td>
<td>Glucocerebrosidase hydrolase</td>
</tr>
</tbody>
</table>
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,³ Naheed Khan,³ Janel Johnson,⁴ Javier Ruiz Martínez,⁹ David Nicholl,¹⁰ Itxaso Martí 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. Singleton⁴,*

Leucine-rich repeat kinase 2 (LRRK2)

Dardarin Protein

Mutations in LRRK2 Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology

Alexander Zimprich,¹,¹¹ 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,⁶ Friedrich Asmús,¹ Bertram Müller-Myhsok,⁹ Dennis W. Dickson,⁴ Thomas Meitinger,³,¹⁰,* Tim M. Strom,³,¹⁰ Zbigniew K. Wszolek,⁵,* and Thomas Gasser¹,*
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
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
Case 1: Lewy body in substantia nigra

Case 2: Lewy body in insular cortex

Case 3: Tau inclusions in substantia nigra

Case 4: Extracellular pigment in substantia nigra

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**
- 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.

LRRK2 G2019S is common & dependent on ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Sporadic</th>
<th>Familial</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N African Arabs</td>
<td>39%</td>
<td>36%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ashkenazi Jews</td>
<td>10%</td>
<td>28%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>UK British</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Welsh</td>
<td>0.3%</td>
<td>1.5%</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

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.
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. Do¹*, Joyce Y. Tung¹, Elizabeth Dorfman¹, Amy K. Kiefer¹, Emily M. Drabant¹, Uta Francke¹, Joanna L. Mountain¹, Samuel M. Goldman², Caroline M. Tanner², J. William Langston², Anne Wojcicki¹, Nicholas Eriksson¹*

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
In 2018, does this change things?

**Cost per Genome**

- **Moore's Law**
- **Illumina wants to sequence your whole genome for $100**
- **NIH National Human Genome Research Institute**
- genome.gov/sequencingcosts
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?
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
Genome-wide association study reveals genetic risk underlying Parkinson’s disease

Javier Simón-Sánchez1,2,22, Claudia Schulte3,22, Jose M Bras1,4,22, Manu Shankar2,22, Coro Pison-Ruiz2, Peter Lichtner6, Sonja W Scholz1,3, Dena G Hernandez1,3, Christine Klein1, Alison Goate8, Joel Perlmutter7, Michael Bonin9, Michael Christian Gieger10, Henry Houlden13, Michael Steffens11, Michael S Okun12, Kelly D Foote12, Hubert H Fernandez12, Bryan J Traynor1, Stefan Schröder12, Katrina Govin19, Marcel van der Brug15, Grisel Lopez18, Stephen J Chung17, Yilkyung Park17, Albert Hollenbeck18, Jianjun Gao19, Xuemei Huang20, Nina Günther Deuschi21, Honglei Chen19, Olaf Riess9, John A Hardy5, Andrew Singleton11, James Gusella11, Michael Hayden14, John Hardy5, Paul J Crow22, and Simon J Sperling1

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 3,363 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 × 10^{-16}, and another at the MAPT locus.

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 1q22 (P = 1.52 × 10^{-12}) and designated this as PARK16, and we also identified BST1 on 4p15 as a second new risk.

forms4. However, mendelian forms of parkinsonism compared to the far more common typical PD, a complex disease caused by multiple genetic and environmental factors2. Association studies have evaluated variants in many candidate genes for PD, including a few, such as common variants of SNCA10 and rare mutations of GBA11, have been identified as PD-susceptibility

forms4. However, mendelian forms of parkinsonism compared to the far more common typical PD, a complex disease caused by multiple genetic and environmental factors2. Association studies have evaluated variants in many candidate genes for PD, including a few, such as common variants of SNCA10 and rare mutations of GBA11, have been identified as PD-susceptibility
Odds Ratios for GBA Mutations among Patients, as Compared with Controls, at Each Study Center and Overall

Clinical Manifestations of Parkinson's Disease in Study Patients with a GBA Mutation and Those without a Mutation


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

- Mutations in \textit{GBA1} can be found in 4% to 7% of PD cases
- Reduced activity of $\beta$-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)
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)