Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Parkinson's disease: new DNA diagnostics

1. Summary of the impact

Research into the genetic causes of Parkinson's disease by Professor Nick Wood's group at the UCL Department of Molecular Neuroscience, describing the mutations in the gene LRRK2, have led to the development of a new genetic test which is now available to patients and their families. This benefits them by providing a precise diagnosis, and an understanding of the risk of disease to relatives. The research has provided new insight into patterns of Parkinson's disease in particular ethnic groups, and given rise to improved public understanding and high profile philanthropy. This discovery has also opened up a new area of research into disease-modifying treatments in Parkinson's disease within the pharmaceutical industry, leading to new drug candidates.

2. Underpinning research

Until approximately 15 years ago, the cause of Parkinson's disease (PD) remained unknown. Since then there has been a huge improvement in our knowledge base. This has largely been driven by findings in genetics. In 2004, researchers at the UCL Department of Molecular Neuroscience, led by Professor Nick Wood were an integral part of the group that first described mutations in the gene LRRK2 **[1]**. Within months of this finding a relatively large number of other reports demonstrated the numerical importance of this gene in the pathogenesis of Parkinson's disease.

However, unique to CNS neurodegenerative disease was our discovery of the so-called common mutation (G2019S) in this gene. This finding in 2005, published in the Lancet, showed for the first time that a relatively rare variant could not only cause familial Parkinson's disease but also plays a very significant role in sporadic Parkinson's disease **[2]**. This finding has been confirmed by numerous groups worldwide and is the basis of a widely available genetic test for this common condition.

For the test to be useful and implementable it was first important to not only provide a clinical phenotype description of the range of the disease features but also the penetrance. The UCL group undertook studies in this area, which were published in 2008 **[3, 4]**. Further studies by international colleagues went on to demonstrate that this mutation was hugely important in certain populations, in particular the Ashkenazi Jewish and North African Berber population. Here the mutation may account for up to one third of Parkinson's cases.

Further genetic analyses **[6]** have shown that common genetic variation at the LRRK2 gene represents a commonly occurring risk factor for non-familial PD, providing further importance to understanding the role this gene plays in PD. Clinico-pathological studies have helped to broaden the phenotype of LRRK2-induced PD and improve diagnostic accuracy **[5]**.

3. References to the research

[1] Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, de Munain AL, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Pena AS, de Silva R, Lees A, Marti-Masso JF, Perez-Tur J*, Wood NW*, Singleton AB*. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron. 2004 Nov 18;44(4):595-600. (*Senior authors) This paper describes the identification of the gene. http://dx.doi.org/10.1016/j.neuron.2004.10.023

[2] Gilks WP, Abou-Sleiman PM, Gandhi S, Jain S, Singleton A, Lees AJ, Shaw K, Bhatia KP, Bonifati V, Quinn NP, Lynch J, Healy DG, Holton JL, Revesz T, Wood NW. A common LRRK2

mutation in idiopathic Parkinson's disease. Lancet. 2005 Jan 29-Feb 4;365(9457):415-6. This first identifies this mutation and implicates it in sporadic disease. http://dx.doi.org/10.1016/S0140-6736(05)17830-1

[3] Khan NL, Jain S, Lynch JM, Pavese N, Abou-Sleiman P, Holton JL, Healy D, Gilks W, Sweeney MG, Ganguly M, Gibbons V, Gandhi S, Vaughan J, Eunson LH, Katzenschlager R, Gayton J, Lennox G, Revesz T, Nicholl D, Bhatia KP, Quinn N, Brooks D, Lees AJ, Davis MB, Piccini P, Singleton AB, Wood NW. Mutations in the gene LRRK2 encoding dardarin (PARK8) cause familial Parkinson's disease: clinical, pathological, olfactory and functional imaging and genetic data. Brain. 2005 Dec;128(Pt 12):2786-96. http://dx.doi.org/10.1093/brain/awh667

[4] Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, Brice A, Aasly J, Zabetian CP, Goldwurm S, Ferreira JJ, Tolosa E, Kay DM, Klein C, Williams DR, Marras C, Lang AE, Wszolek ZK, Berciano J, Schapira AH, Lynch T, Bhatia KP, Gasser T, Lees AJ, Wood NW; on behalf of the International LRRK2 Consortium. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurology. 2008 Jul;7(7):583-90. This provides the groundwork to permit clinical adoption of this mutation testing into clinical practice. http://dx.doi.org/10.1016/S1474-4422(08)70117-0

[5] Silveira-Moriyama L, Guedes LC, Kingsbury A, Ayling H, Shaw K, Barbosa ER, Bonifati V, Quinn NP, Abou-Sleiman P, Wood NW, Petrie A, Sampaio C, Ferreira JJ, Holton J, Revesz T, Lees AJ. Hyposmia in G2019S LRRK2-related parkinsonism: clinical and pathologic data. Neurology. 2008 Sep 23;71(13):1021-6. http://dx.doi.org/10.1212/01.wnl.0000326575.20829.45

[6] International Parkinson Disease Genomics Consortium, Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM, Saad M, Simón-Sánchez J, Schulte C, Lesage S, Sveinbjörnsdóttir S, Stefánsson K, Martinez M, Hardy J, Heutink P, Brice A, Gasser T, Singleton AB, Wood NW. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet. 2011 Feb 19;377(9766):641-9. Epub 2011 Feb 1. http://dx.doi.org/10.1016/S0140-6736(10)62345-8

4. Details of the impact

The research results described above represent a significant shift in understanding of a condition that for many years had been taught to medical students as the prime example of a non-genetic disease. As a result of our research, a new genetic test is now available to patients and their families. It is provided at 17 laboratories, both in the UK and internationally **[a]**. The practice is based on the data and methods first used by the UCL group (references [2] and [4] above). Therefore these findings have had a direct impact on the practice and implementation of this mutation test. This is the first time in Parkinson's disease that tests have been widely available and have been useful to a large number of potential sufferers. At our laboratory, affiliated with the National Hospital for Neurology and Neuroscience, we have conducted 760 tests in the period 2008-13 **[b]**. The UK Genetic Testing network approved an evaluation of the test for LKKR2 as a genetic test for the NHS Service Gene Dossier in 2011 **[c]**.

The test gives patients a precise diagnosis, and understanding of the risk of disease to relatives, with the possibility of pre-symptomatic testing in those at risk. Prenatal testing is also a possibility. To a lesser degree, an understanding of the mutation may help the prognosis of the disease **[d]**. One patient, Genia Brin (see more below), described the impact of the test results as follows: "*When I got the results I thought 'that's why'. There was some sense of relief to know there was a reason behind the illness*" **[e]**.

Wood has been actively involved in raising public awareness of the genetic basis of Parkinson's disease, and his videos on YouTube have attracted hundreds of viewings **[f]**.

Many other research groups have built on our early work, and one area of particular interest is the identification of the specific relevance of the mutation to particular ethnic groups, for example

Ashkenazi Jewish and North African Arab populations **[g, h]**. The link was highlighted in the Jewish Chronicle, Pittsburgh **[i]**.

The internet entrepreneur Sergey Brin blogged in 2008 about his experience of the LKKR2 mutation being discovered in his family, through his involvement with the genetic testing company 23andMe, saying "*I carry the G2019S mutation and when my mother checked her account, she saw she carries it too…it is clear that I have a markedly higher chance of developing Parkinson's in my lifetime than the average person…research into LRRK2 looks intriguing (both for LRRK2 carriers and potentially for others). This leaves me in a rather unique position. I know early in my life something I am substantially predisposed to. I now have the opportunity to adjust my life to reduce those odds (e.g. there is evidence that exercise may be protective against Parkinson's). I also have the opportunity to perform and support research into this disease long before it may affect me. And, regardless of my own health it can help my family members as well as others*." **[j]** LRRK2 has become a priority area for the Michael J. Fox Foundation for Parkinson's research, which, together with the Brin Wojcicki Foundation, has invested more than $44 million in research projects in this area to June 2012 **[k].** This high profile support has raised public awareness of the area, evidenced by press coverage **[j].**

More broadly speaking, this work has had a wider impact on the rare diseases agenda. The identification of this mutation in a common disease provides a strong motivation for the recently announced rare disease initiative within the NIHR Rare Diseases Translational Research Collaboration **[l]**. It is highly likely that similar mutations or variants will be identified in other common diseases. The pathway to genetic implementation and diagnostics is now well established and will be followed by many of these other conditions using the paradigm described above.

As a common mutation within the LRRK2 gene, it has also formed the mainstay of much of the biological exploration that has been carried out of the functioning of this gene and has also been a focus for many major pharmaceutical companies including GlaxoSmithKline (GSK) and Eisai. GSK and Eisai are well advanced in producing LRRK2 kinase inhibitors based on biological investigations of this mutation **[m]**. GSK reported the discovery and characterization of 2-arylmethyloxy-5-subtitutent-N-arylbenzamides with potent LRRK2 activities in 2012, and have been conducting an observational study to fully characterise the neurocognitive phenotype of Parkinson Disease patients with LRRK2 mutation since 2011 **[n].**

There is widespread expectation that these molecules will be trialled in the at-risk population within the next 2-3 years. If successful this would provide the first disease-modifying treatments in Parkinson's disease and would be based firmly on knowledge of the biology and as direct result of the primary discoveries of the UCL group.

5. Sources to corroborate the impact

[a] There are now 17 laboratories Worldwide who are offering this gene test, which are listed here: http://www.genetests.org/ Examples include:

- Athena Diagnostics: http://www.athenadiagnostics.com/content/test-catalog/find-test/service-detail/q/id/369
- EDDNAL http://www.eddnal.com/directory/result.php?disease=3158
- Gene Tests: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/250809?db=genetests
- Orphanet: http://www.orpha.net/consor/cgi-bin/ClinicalLabs_Search_Simple.php?lng=EN&LnkId=932&Typ=Pat
- UK GTN: http://ukgtn.nhs.uk/

[b] Can be corroborated by the Head of National Hospital for Neurology and Neurosurgery diagnostic lab. Contact details provided.

[c] http://ukgtn.nhs.uk/uploads/tx_ukgtn/PARK8_LRRK2_GD_Sept_11.pdf

[d] Healy DG, Wood NW, Schapira AH. Test for LRRK2 mutations in patients with Parkinson's disease. Pract Neurol. 2008 Dec;8(6):381-5. http://dx.doi.org/10.1136/jnnp.2008.162420

[e] http://www.nwpf.org/News.aspx?Item=4050.

[f] Public engagement work:
- The genetics of LRRK2, Presentation at a meeting of the Biochemical Society in 2012: http://youtu.be/Ze3DPKP6Je8
- Understanding the Genetics of Parkinson Disease, from the workshop 'brains in dialogue on genetic testing', Trieste, 28-29 January 2010, Trieste, Italy. www.youtube.com/watch?v=O9fFZcD5cU0

[g] Lesage S, Dürr A, Tazir M, Lohmann E, Leutenegger AL, Janin S, Pollak P, Brice A; French Parkinson's Disease Genetics Study Group. LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. N Engl J Med. 2006 Jan 26;354(4):422-3. http://dx.doi.org/10.1056/NEJMc055540

[h] Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, Hunt AL, Klein C, Henick B, Hailpern SM, Lipton RB, Soto-Valencia J, Risch N, Bressman SB. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2006 Jan 26;354(4):424-5. http://dx.doi.org/10.1056/NEJMc055509

[i] http://thejewishchronicle.net/view/full_story/12893942/article-Parkinson's-treatments-on-the-horizon-as-Ashkenazi-Jews-cope-with-the-disease-?instance=lead_story_left_column

[j] Sergey Brin's blog post: http://too.blogspot.co.uk/2008/09/lrrk2.html
Further press coverage:
http://www.guardian.co.uk/technology/2008/sep/19/sergey.brin.google
http://www.wired.com/magazine/2010/06/ff_sergeys_search/all/

[k] Michael J Fox Foundation for Parkinon's Disease Priority area:
https://www.michaeljfox.org/research/priority-area-detail.php?lrrk2
https://www.michaeljfox.org/foundation/publication-detail.html?id=253&category=4

[l] http://www.uclhospitals.brc.nihr.ac.uk/news/brc-professors-lead-themes-new-nihr-partnership

[m] The programmes on producing LRRK2 kinase inhibitors at GSK can be corroborated by the Director of External Alliances & Development, R&D China at GSK. Contact details provided.

[n] Reith AD, Bamborough P, Jandu K, Andreotti D, Mensah L, Dossang P, Choi HG, Deng X, Zhang J, Alessi DR, Gray NS. GSK2578215A; a potent and highly selective 2-arylmethyloxy-5-substitutent-N-arylbenzamide LRRK2 kinase inhibitor. Bioorg Med Chem Lett. 2012 Sep 1;22(17):5625-9. http://dx.doi.org/10.1016/j.bmcl.2012.06.104.
http://clinicaltrials.gov/show/NCT01424475