INTERVIEW

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The genetics of Parkinson's disease: piecing together the jigsaw

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Nicholas Wood[†]: Nicholas Wood is Galton Professor of Genetics and Head of the Department of Molecular Neuroscience at the UCL Institute of Neurology (London, UK). He qualified in Medicine from Birmingham University (UK) in 1986 and undertook doctoral research at the University of Cambridge (UK) and was awarded a PhD in 1994. He has been a Senior Lecturer, Reader and Professor at the Institute of Neurology since 1995. In 2004, he was made a Fellow of the Academy of Medical Sciences. His primary research interest is the genetics of neurological disease with an emphasis on the genetics of Parkinson's disease and the ataxias. He has published over 270 peer-reviewed articles and is on the board of several international neuroscience journals.

Q You were involved in the discovery of the involvement of the *PINK1* gene in Parkinson's disease in 2004; how unexpected was the involvement of this gene?

The short answer is that the involvement of almost any gene is a bit unexpected; this is probably the case for 90% of genes that are found to be related to a disease. However, what was particularly interesting about this discovery was what it started to indicate in terms of disease pathogenesis; namely, that this is a protein that is directed towards mitochondria, and therefore the involvement of mitochondria started to look a lot more interesting again. People had been thinking about mitochondria for a few decades, but until that point nobody had found definitive proof of their involvement, in my view. The involvement of *PINK1* clearly showed that a nuclear-encoded gene could indicate that the mitochondria were abnormal. Since that discovery a lot of effort has been directed to investigating the mitochondrial story in Parkinson's disease, and other genes have been tied into that possible pathway – this has emerged as a very interesting field.

Q What impact did this discovery have on the field of Parkinson's disease research?

First, this gave us another gene to build into our picture of Parkinson's disease. This is the case for every gene that is discovered to have an involvement – questions need to be asked about how the new gene fits into the existing picture. Most of the time, even for some years after finding a gene, it is still not clear how it ties in. We are getting better and slightly quicker at doing this, but it is a real challenge. Another piece of the jigsaw has been found, but we have no idea how many pieces there should be or how they fit together, if at all.

Second, as the name suggests, *PINK1* is a kinase, or possible kinase, and is therefore involved in transferring phosphate groups to proteins. So, the big question is determining what the target, or targets, is of *PINK1* – this is still being investigated.

Q How has our understanding of the genetic basis of Parkinson's disease evolved over the past few years?

Our understanding has evolved massively, and this has been truly remarkable. It has actually changed more than anybody, even

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[†]UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK;
Tel: +44 207 837 3611; Fax: +44 207 278 5616; n.wood@ucl.ac.uk

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the most partisan geneticist, would have predicted. You now cannot think about Parkinson's disease without thinking about how the genetics fit in and what they tell us.

However, the other truth is that despite the progress, genetics still only explains a relatively modest proportion of cases. So, there is still some way to go and quite a lot that is not yet understood about the genetics of Parkinson's disease. There would be a big debate among my colleagues about how much weight can be given to genetics; some would say 10%, some would say 20%, others would say as high as 50%, which is clearly a wide range. I do not think anybody would say there is a 100% involvement, but equally nobody would now say it is 0 or 5%, which is what some thought up until 5–10 years ago. So, it is clear there has been progress.

The other reason to being reasonably optimistic is that there are now 15–16 genes or genetic factors to investigate and try to determine the importance of, so the jigsaw is looking a little fuller! We have the chance, as with all jigsaws, of making it all fit together. However, this will be a big task, and it will not be achieved in the next 2 or 3 years; it is going to be a number of years before the picture becomes clearer.

Q What research needs to be carried out to further define the role of *PINK1* in Parkinson's disease?

A greater delineation of the pathways is needed, to determine what regulates PINK1 activity and what PINK1 regulates or influences in turn. We need to determine where PINK1 fits into the molecular pathway, and what the upstream and downstream consequences are of having either normal *PINK1* or abnormal *PINK1* in the case of patients with the disease.

Q Your research is now making use of a genome-wide approach. What are the advantages of this method over candidate gene studies?

With genome-wide association studies (GWAS) you are not confined to your own belief system or the evidence of others. You can robustly and very comprehensively assay the variability in the whole genome and, if you have the right study design,

determine with a fair degree of certainty whether you have found something or, in fact, excluded something (GWAS can help determine where not to look for things). In the last few years the rigor and comprehensive nature of GWAS have added to our understanding of disease; Parkinson's disease in this instance, but also multiple sclerosis, amyotrophic lateral sclerosis and a whole host of other diseases.

Candidate gene studies start with a gene that is thought to be important, which is then tested; from this you might find it is involved or you might find that it is not. In addition, that is just a tiny fraction of the genome, compared with a GWAS that assays the whole genome. However, in assaying the whole genome, the statistical space you are going into is vast, and a very large scale is needed for this type of study.

Q You recently published the results of a GWAS [1] conducted with Parkinson's disease patients and controls, followed by a meta-analysis paper [2] – briefly, could you describe the main findings presented in these papers?

The GWAS paper involved just fewer than 2000 cases and approximately 5000 controls, so it was on quite a large scale [1]. Each sample was genotyped for approximately 600,000 polymorphisms, generating a huge amount of data and showing that a number of genes were implicated in Parkinson's disease. Tau and α -synuclein were the most prominent, but there were suggestions that two or three others might be important. The reason for saying 'might' is that although 2000 patients is a lot, it cannot be compared with a study involving 10,000 or 20,000; it is not possible to be certain whether a larger study might uncover other examples.

The second paper is a meta-analysis of a larger scale study in which the results from our 2000 patients were combined with patients from the USA, Germany, France, The Netherlands and Iceland, totaling nearly 10,000 cases and 12,000 controls [2]. Owing to the larger sample size the meta-analysis resulted in quite a large number of genes of potential interest, in this case up to 15–20 genes that looked quite interesting. This was then replicated

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in a fresh 5000–6000 sample size, which led to the identification of at least five new genes. A total of 11 genes are discussed in this paper; of course, tau and α -synuclein were identified again, and the p-values for those were massive. Of the other nine genes, some had been discussed in previous papers, although none had been absolutely confirmed. In addition, five absolutely new genes were identified that nobody had discussed before.

Q There are important societal consequences to the discovery of data related to disease risk such as this. How successfully do you think information is relayed to the public at present? How does this need to evolve in the future?

This is a very important matter, but it is difficult to do well. It is easy to lose people even in a one-to-one conversation on the topic, so trying to achieve understanding with a population that you are not engaging with is even harder. For example, in some ways *PINK1* is easy to understand – primary mutations knock down the function of PINK1, and when that happens it is bad for you and you develop Parkinson's disease – a lot of people can understand that. However, the GWAS have identified variations that many of us might have, but even if a person has all the risk factors that we now know about, they would only have three- or maybe four-times the risk of developing Parkinson's disease. Given that the overall population risk is 1%, this would mean their risk would go up to 3%, if they have all the known risk factors. Given the complexity of this, it is not easy to get across and ensure understanding, but it is what we need to work towards. We, and others, are keen to make our results accessible to scientists, but also to disseminate the information in a more lay accessible, digestible form, so people can start to understand and engage in this topic. This is a tough job, it is not easy to do, but it is what we need to and are trying to do.

Q Finally, where will you be focusing your research over the next 5 years?

There are two key areas of focus. First, it is necessary to identify all the other familial, mendelian mutations that are involved in Parkinson's disease and determine how many more major genes are involved. A clear strategy is needed to identify these, to ensure we have a full, familial Parkinson's disease picture.

Second, regarding the GWAS follow-up, once a variant gene or locus associated with the disease is identified, it is important to determine what that gene or locus is actually marking, to determine which gene and, more importantly, what genomic event is occurring – is the gene being upregulated, switched off, is its splicing being altered, for example. We need to create a complete picture of the genomic events that might be impacted by these associations, in order to better model the biology of the disease.

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