

4. Annemarie Opprecht Parkinson Award 2008

Parkinson's disease: where are we up to in understanding the causes of the disease and how does this work fit in?

Over the last ten years, we have made great strides in developing an understanding of the causes of Parkinson's disease. Six genes for the disease have been discovered: α -Synuclein (which is the major component of Lewy bodies), LRRK2 (which is a regulatory molecule), GBA (which is involved in the metabolism of membranes), and parkin, PINK1 and DJ-1 (which are all involved in mitochondrial metabolism). Although these findings have been very informative in terms of developing an understanding of the biochemical pathways which lead to the disease pathology, together, they only account for >10% of cases of Parkinson's disease. In general, we believe that most cases of disease are caused by a mixture of genetic risk factors interacting with the environment.

Until this last 3 years, there has been no clear way to find genes which increase the risk of disease. But now, through the sequencing of the human genome and the development of a catalogue of common human genetic variability ("the HapMap"), we can now assess the entire human genome for its contribution to the risk of getting disease through a process called a "whole genome association study".

Singleton and Hardy published the first attempt to use this technology for a neurological illness in their paper on Parkinson's disease, and this is clearly a large step forward. They published on 300 cases and controls, and they made the data publicly available: this was the very first time that the data from such a study (in any disease) had been made freely publicly available and has now set the standard for such studies. It is important that the data is freely available because that means that, as they and others, do further studies on Parkinson's disease, they can add the data to the Singleton/Hardy database to identify new risk genes. They have gone on with collaborators to examine many more samples (~5000) and Dr. Singleton will discuss these exciting developments at the Awards. One clear finding is that genetic variability in the production of synuclein is a risk for developing the common form of the disease: a finding which follows on from their discovery of a few families with synuclein gene duplications 5 years ago.

In parallel with the public deposition of genetic data which is beginning to allow us to understand the genes involved in typical Parkinson's disease, Hardy and Singleton have also worked to put together databases of human brain gene expression and these latter are complementary to the gene database as they allow researchers to understand how risk genes lead to disease by being over or underexpressed.

A theme of their work, which is also a more general theme of how research is now progressing, is the creation of databases which allow researchers unconnected with the original design and execution of scientific experiments, to analyse the data, and this will undoubtedly speed progress in research into Parkinson's disease and other common neurological conditions.

Reading List

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