



Ubiquitin links Parkinson's disease genes

a tantalizing link between two new genes

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Although we have known about Parkinson's disease for almost 200 years (it was discovered by the English physician James Parkinson in 1817), the role of genetics in the pathology of the disease has only recently emerged.

Two new genes associated with Parkinson's disease have been reported. The first, called α -synuclein, is mutated in an autosomal-dominant type of Parkinson's disease. The second, uncovered in April 1998, codes for a protein called parkin, which is associated with a juvenile autosomal-recessive form of Parkinson's disease (AR-JP).

One of the pathological features of most types of Parkinson's disease is the appearance of an inclusion body, known as a Lewy body, in many regions of the brain. The Lewy body is associated with neuronal degeneration and is also seen in Alzheimer's disease. It may be no coincidence that α -synuclein is found in Lewy bodies. In AR-JP, however, there is no Lewy body formation. In spite of these apparent differences between these two types of Parkinson's disease, there are some tantalizing links at the molecular level.

The best way to visualize Lewy bodies in brain tissue is to use antibodies against ubiquitin, because they contain high levels of ubiquitinated proteins. In cells, ubiquitin first binds to proteins displaying degradation signals, then recruits additional ubiquitin molecules to form a polyubiquitin chain. This 'flags' the protein for destruction by the 26S proteasome. In neurodegenerative disease, incompletely degraded, ubiquitinated proteins accumulate in Lewy bodies. It is intriguing that α -synuclein, which is responsible for a subset of cases of Parkinson's disease, should be found in the same place.

Enter parkin. After cloning and sequencing the suspected Parkinson's disease gene, the researchers compared their sequence to those in the database. They found that parkin contains an ubiquitin-like domain and a RING finger motif, implicated in interactions with DNA (and more recently, with other proteins). Could parkin function in a similar way to ubiquitin proteins, and could its defect in AR-JP interfere with the ubiquitin-mediated protein degradation pathway?

Although all roads (for the present) lead to a defect in ubiquitin-mediated pathways as a cause of Parkinson's and perhaps other neurodegenerative diseases, the two types of Parkinson's disease described here account for only a small fraction of the total number of Parkinson's disease cases. However, these early forays will prove extremely valuable for tracking down other genetic factors that could be involved in neurodegenerative disease.

Search PubMed for the role of alpha-synuclein.

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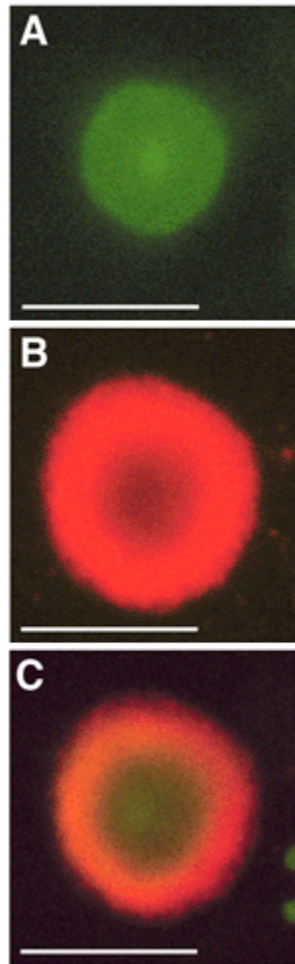
What role do alpha-synuclein and parkin play in Parkinson's disease?

Use BLAST to search for parkin.

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Protein that match parkin give clues to its function

**Lewy bodies visualized by staining for ubiquitin.**

Lewy bodies, found in Parkinson's disease brain and other related neurodegenerative disorders, can be visualized by staining for ubiquitin.

(A) An antibody against ubiquitin stains Lewy bodies green.

(B) A red stain for alpha-synuclein.

(C) If both ubiquitin and alpha-synuclein are found in the same place, the green and red stains combine to give a yellow/orange color. This demonstrates that alpha-synuclein and ubiquitin cluster in the same place - a tantalizing parallel with parkin, which has been found to be similar to ubiquitin proteins.

The ubiquitin family of proteins are known to be involved in the pathogenesis of a number of neurodegenerative disease, including Alzheimer's disease, where they are a component of paired helical filaments.