NEURODEGENERATIVE DISEASE

DCTN1 mutations are associated with Perry syndrome

The *DCTN1* gene codes for the large subunit of dynactin, which is involved in microtubule-associated intracellular transport. In *Nature Genetics*, Matthew Farrer *et al.* report the identification of five novel mutations within exon 2 of *DCTN1* that are associated with the neurodegenerative disease Perry syndrome. Interestingly, a previously identified mutation (Gly59Ser) within exon 2 was implicated in a case of familial motor neuron disease. “There is no motor neuron involvement in Perry families,” states Farrer. “It is primarily an extrapyramidal [system] syndrome.”

Perry syndrome is a rare, autosomal-dominant, neurodegenerative disorder characterized clinically by early-onset parkinsonism, weight loss, depression and hypoventilation. At the pathological level, TDP-43 (transactive-response DNA-binding protein 43) neuronal inclusions can be observed that resemble those present in amyotrophic lateral sclerosis and frontal temporal dementia. The distribution of TDP-43 inclusions differs between these neurological conditions, however, and in Perry syndrome cortical areas and motor neurons remain largely unaffected.

The researchers collected clinical data and blood samples from the eight families, worldwide, in which Perry syndrome is recognized. Following genome-wide scanning and linkage analysis, the five disease-segregating missense mutations were identified. With the exception of

Figure 1 | Distribution of the overexpressed dynactin large subunit in COS-7 cells. **a** | Wildtype dynactin large subunit and **b** | Perry syndrome mutant dynactin large subunit. Permission obtained from Dr Justus C. Daechsel.

individuals from one family, all of these mutations were associated with remarkably similar disease phenotypes, both clinically and pathologically.

Dynactin is important for intracellular transport, and the Gly59Ser mutation and the novel *DCTN1* mutations are known to encode changes to amino acids within the ‘CAP -Gly’ domain of the dynactin large subunit. This region of dynactin is involved in protein–protein interactions with components of the cytoskeleton. Preliminary functional studies reported in this paper demonstrate that two of the novel mutations, like Gly59Ser, impair normal dynactin–microtubule binding and alter the distribution of dynactin within

cells (Figure 1). The exact relevance of these results to the underlying molecular pathology of the disease remains to be fully established.

The challenges ahead for the researchers include understanding how mutations that affect subtly different regions of the CAP-Gly domain lead to the targeting of different neuronal populations, and examining the relationship between mutant dynactin and TDP-43 in the disease process.

Darran Yates

Original article Farrer, M. J. *et al.* *DCTN1* mutations in Perry syndrome. *Nat. Genet.* **41**, 163–165 (2009).