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## GUEST EDITORIAL

# Lewy body diseases and multiple system atrophy as α-synucleinopathies

Parkinson's disease and dementia with Lewy bodies are among the most common neurodegenerative diseases. They share the Lewy body and the Lewy neurite as their defining neuropathological characteristics. Originally described in 1912 as a light-microscopic entity, the Lewy body was shown to be made of abnormal filaments in the 1960s. Over the past year, the biochemical nature of the Lewy body filament has been revealed.

A large number of different proteins has been reported to be present in Lewy bodies and Lewy neurites by immunohistochemical methods. However, these findings do not permit us to distinguish between intrinsic Lewy body components and normal cellular constituents that get merely trapped in the filaments that make up the Lewy body. A similar problem plagued the field of the neurofibrillary lesions of Alzheimer's disease over part of the 1980s. It was solved with the purification and analysis of paired helical and straight filaments, the filamentous constituents of the neurofibrillary lesions. Unfortunately, a similar approach with Lewy bodies has only met with partial success, mainly because Lewy bodies and Lewy neurites are much less abundant than neurofibrillary lesions.

This was the situation until the middle of last year, when genetics came to the rescue, taking us straight to the very core of the Lewy body filament. In June 1997, Polymeropoulos *et al* reported a missense mutation in α-synuclein in a large pedigree with early-onset Parkinson's disease and in three smaller, apparently unrelated kindreds.[1] The mutation is an alanine to threonine change at residue 53 of α-synuclein, an abundant 140-amino acid presynaptic protein of unknown function. Somewhat surprisingly, rodent and zebrafinch α-synucleins carry a threonine residue at position 53, like the mutated human protein. This, together with the fact that all families with the A53T mutation are of either Southern Italian or Greek origin, and that this part of Italy was colonized by Greece a long time ago, led some to propose that the A53T change may be nothing more than a rare benign polymorphism. However, the discovery earlier this year of an alanine to proline mutation at residue 30 of α-synuclein in a family of German descent with Parkinson's disease,[2] has settled this controversy in favour of the relevance of α-synuclein for the aetiology and pathogenesis of some familial cases of Parkinson's disease. The two mutations in α-synuclein are the first known genetic causes of Parkinson's disease. They are located in the amino-terminal half of α-synuclein, which consists of seven imperfect repeats of 11 amino acids each, with the consensus sequence KTKEGV (Figure 1). It has been suggested that α-synuclein may bind through these repeats to membranes rich in acidic phospholipids.[3]

This work raised the question whether α-synuclein is a component of Lewy bodies and Lewy neurites of idiopathic Parkinson's disease and of dementia with Lewy bodies. Using well-characterised anti-α-synuclein antibodies, Spillantini *et al* showed strong staining of both Lewy bodies and Lewy neurites in idiopathic Parkinson's disease and dementia with Lewy bodies.[4] They also reported the lack of staining of these pathological structures with an antibody directed against the related β-synuclein. Several subsequent papers,[5–8] one of which is published by Mezey *et al* in this issue of *Molecular Psychiatry*[9] have reported similar results. All studies to date have shown strong staining of Lewy bodies and Lewy neurites in every case of Parkinson's disease and dementia with Lewy bodies investigated. Paradoxically, there have been no reports so far on the staining for α-synuclein of Lewy bodies and Lewy neurites in brain tissue from individuals with the A53T or A30P mutations.

Several studies have shown that the staining of Lewy bodies and Lewy neurites for α-synuclein is more extensive than the staining for ubiquitin,[7,8,10] until now the most sensitive immunohistochemical marker. This implies that ubiquitination is a later event than accumulation of α-synuclein and means that staining for α-synuclein will replace staining for ubiquitin as the preferred means for identifying Lewy bodies and Lewy neurites in tissue sections. In dementia with Lewy bodies, the Lewy body pathology frequently coexists with a neurofibrillary pathology like that found in Alzheimer's disease. Ubiquitin antibodies stain both the Lewy body and the neurofibrillary pathologies. By contrast, α-synuclein antibodies only stain the Lewy body pathology, whereas anti-tau antibodies only stain the neurofibrillary pathology.

Taken together, the genetic and the neuropathological evidence suggests, but does not prove, that α-synuclein is a major component of the abnormal filaments that make up Lewy bodies and Lewy neurites. Two recent studies have investigated this question directly by immunoelectron microscopy of filaments from purified Lewy bodies,[7] or of sarcosyl-insoluble filaments extracted from cingulate cortex of patients with dementia with Lewy bodies.[10] Both studies have demonstrated strong labelling of filaments with α-synuclein

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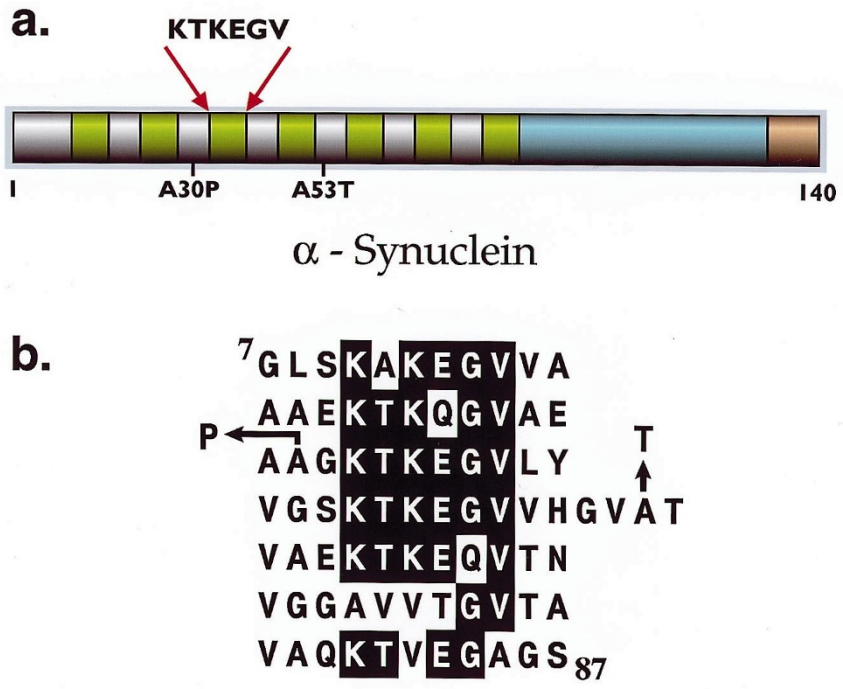


**Figure 1** Mutations in the α-synuclein gene in familial Parkinson's disease. (a) Schematic diagram of human α-synuclein. The seven repeats with the consensus sequence KTKEGV are shown as green bars. The hydrophobic region is shown in blue and the negatively charged carboxy-terminus in red. The two known missense mutations are indicated. (b) Repeats in human α-synuclein. Residues 7–87 of the 140-amino acid protein are shown. Amino acid identities between at least five of the seven repeats are indicated by black bars. The alanine to proline mutation at residue 30 between repeats two and three and the alanine to threonine mutation at residue 53 between repeats four and five are shown.

antibodies. They provide the first demonstrations of the morphologies of α-synuclein filaments. Baba *et al* also provided the first immunoblot analysis of α-synuclein from purified Lewy bodies.[7] Interestingly, in addition to full-length α-synuclein, truncated proteins were also found. The nature and significance of the truncations in α-synuclein remain to be determined.

Sarcosyl-insoluble α-synuclein filaments have a diameter of 5–10 nm.[10] They were labelled along their entirety by an antibody which recognises the carboxy-terminal region of α-synuclein, indicating that they contain α-synuclein as a major component (Figure 2). The filament morphologies are consistent with a model in which the α-synuclein molecules assemble to form a 5-nm protofilament, two of which could associate to produce a variably twisted filament. It suggests that α-synuclein molecules, which are believed to be extended and relatively unstructured,[11] may run parallel to the filament axis. This differs from the packing of tau protein in filaments from Alzheimer's disease and other tauopathies, where individual tau molecules are believed to run mainly perpendicular to the filament axis. An antibody which recognises amino acids 11–34 of α-synuclein only ever labelled one filament end.[10] This suggests that the epitope of this antibody is buried in the body of the filament and exposed only at one end and that α-synuclein filaments are polar structures. The recent immunoelectron microscopy work leaves little doubt that α-synuclein is the major component of Lewy body filaments. It follows that Parkinson's disease and dementia with Lewy bodies are α-synucleinopathies.

Several groups have looked at the possible presence of α-synuclein in the filamentous inclusions of other neurodegenerative diseases, resulting in the discovery that multiple system atrophy (MSA) is a third α-synucleinopathy.[12–14] Neuropathologically, glial cytoplasmic inclusions, which consist of filamentous aggregates, are the defining feature of MSA. They are found mostly in the cytoplasm and, to a lesser extent, the nuclei of oligodendrocytes. Inclusions are also observed in the cytoplasm and nuclei of some nerve cells, as well as in neuropil threads. They consist of straight and twisted filaments, with reported diameters of 10–30 nm. Until very recently, the biochemical composition of MSA filaments was unknown.

This has changed with the discovery that glial cytoplasmic inclusions are strongly immunoreactive for α-synuclein[12–14] and that filaments from brains of patients with MSA are strongly labelled by α-synuclein antibodies.[14] Filament morphologies and antibody labelling characteristics are very similar to those of the α-synuclein filaments from dementia with Lewy bodies.[10,14] This work indicates that α-synuclein is the major component of MSA filaments and reveals an unexpected molecular link between MSA and Lewy body diseases.

It appears likely that nerve cells and glial cells

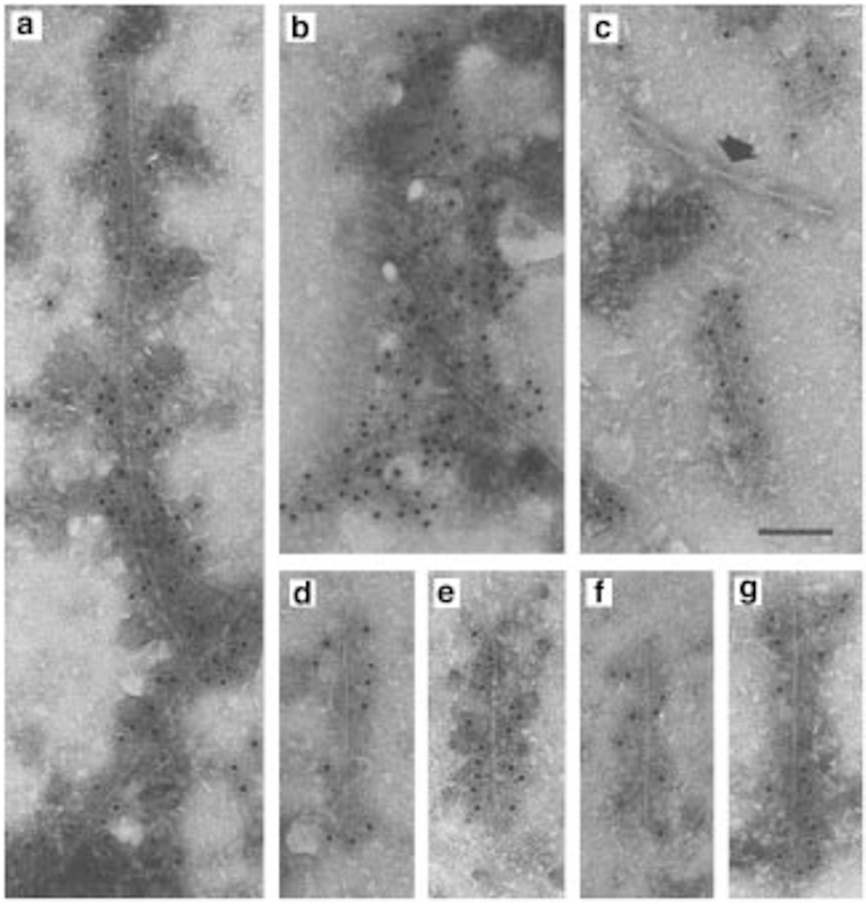


**Figure 2** Filaments from cingulate cortex of patients with dementia with Lewy bodies immunolabelled for $\alpha$-synuclein. (a and b) Small clumps of labelled $\alpha$-synuclein filaments. (c) A labelled $\alpha$-synuclein filament and an unlabelled paired helical filament (arrow). The labelled filaments have various morphologies, including: 5-nm filament (d); 10-nm filament with dark stain penetrating centre line (e); twisted filament showing alternating width (f); 10-nm filament with slender 5-nm extensions at ends (g, also c). Scale bar, 100 nm (in c) (from Reference 10).

degenerate in Parkinson's disease, dementia with Lewy bodies and multiple system atrophy, because of the presence of abnormal $\alpha$-synuclein filaments. It follows that the events that lead to assembly of the normally soluble $\alpha$-synuclein into insoluble, ordered filamentous assemblies constitute the seminal pathological event in these diseases. At present, the mechanisms that lead to filament assembly are unknown. If recent progress is anything to go by, it should not be long before we understand $\alpha$-synuclein assembly. This may ultimately lead to the development of novel, more effective ways to treat these diseases.

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