***LRP10*: a novel disease gene bridging Parkinson’s Disease and Dementia with Lewy Body**

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Clinical, neuropathological and neurochemical features have led to the hypothesis that Parkinson’s disease, Parkinson’s disease dementia (PDD) and dementia with Lewy bodies (DLB) might represent different manifestations of the same disease1. The common hallmark of these entities is α-synuclein/Lewy bodies pathology, along with tau and Aβ plaque pathology which seem the best predictor for dementia onset2.

Yet, merging these syndromes in one single disease entity still represents a controversial issue3. Indeed, based on the clinic-pathological overlap, the MDS Task Force on the Definition of Parkinson’s Disease has introduced the diagnostic category of “PD (DLB subtype)” for those DLB patients who present with motor signs and meets full clinical criteria for PD4.

Heterozygous mutations in *SNCA* (encoding α-synuclein) and *GBA* (encoding glucocerebrosidase) have been implicated in the pathogenesis of PD, PDD and LBD, supporting the view that these disorders represent a continuum rather than distinct entities. Now, a recent study published in The Lancet Neurology has identified heterozygous pathogenic variants in a novel gene, *LRP10* (encoding the LDL Receptor Related Protein 10), associated to autosomal dominant PD, PDD and LBD5. The key family which led to identify the gene by a consequential approach of genome-wide linkage analysis and whole exome sequencing is a large Italian pedigree with 13 members affected by PD and 1 affected by DLB.

Eight additional patients from a large international multicentre series diagnosed with PD, PDD or LBDwere subsequently found to carry *LRP10* variants. Three of these variants were detected in brain DNA samples from the 168 probands with pathological confirmation, all showing marked accumulation of α-synuclein. Analysis of gene sequencing data from a Dutch study of 645 patients with abdominal aortic aneurysms disclosed only one carrier, whose neurological status was unknown. Finally, in stage three of the study, a molecular screening of *LRP10* in an independent series of 1466 PD patients and 811 healthy controls demonstrated two further variants in three patients (from Sardinia and Taiwan) and none of the controls. Functional studies showed reduced expression or functioning of most mutants, suggesting that haploinsufficiency of *LRP10* might promote alpha-synuclein mediated neurodegeneration.

Although its function is largely unknown, LRP10 has been implicated in trafficking between the transGolgi network and endosomes and could be involved in regulation of alpha-synuclein aggregation and cell-to-cell transmission. Thus, LRP10 adds to the still limited number of genes whose variants were confidently demonstrated to cause the full spectrum of synucleinopathies, opening novel intriguing windows on the pathogenetic mechanisms underlying these disorders. Further studies are needed to understand which specific pathogenetic mechanisms are triggered by LRP10 variants and which additional genetic and environmental factors interact with these variants to produce a phenotype ranging from PD to DLB.

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