Involvement of striatal motoric subregions in familial frontotemporal dementia with parkinsonism harboring the C9orf72 repeat expansions

Li Liu¹ | Shuying Liu¹ | Min Chu¹ | Kexin Xie¹ | Yue Cui¹ | Pedro Rosa-Neto² | Liyong Wu¹

¹Xuanwu Hospital, Capital Medical University, Beijing, China
²McGill University Research Centre for Studies in Aging, Montreal, QC, Canada

Abstract

Background: The chromosome 9 open reading frame 72 (C9ORF72) has been proposed as the causative gene of frontotemporal dementia with parkinsonism (FTDP), but its pathophysiological mechanism of parkinsonism is poorly understood.

Method: To explore the roles of striatal motor subdivisions in the pathogenesis of parkinsonism resulting from C9ORF72 repeat expansions in the FTDP, two patients with FTDP from one pedigree and seventeen healthy controls were enrolled. The participants received clinical interviews and underwent neuropsychological assessments, genetic testing, [¹⁸F]-fluorodeoxyglucose PET/MRI, and [¹⁸F]-dihydrotetrabenazine PET/CT. Voxel-wise and region of interest analysis were conducted with respect to gray matter volume, metabolism, and dopamine transport function between patients and controls, focusing on the motor part of the striatum according to the Oxford-GSK-Imanova Striatal Connectivity Atlas.

Result: Patient 1 presented with parkinsonism as the initial symptom, while patient 2 exhibited behavior disturbance as the first symptom, followed by parkinsonism within one year. Both patients had the hexanucleotide expansion detected in C9ORF72 (>52 repeats). Gray matter volume atrophy, hypometabolism and dopamine dysfunction were observed in the motor areas of the striatum. Of the two patients, marked glucose hypometabolism within the striatal motor subregion was observed in patient 1, with corresponding gray matter atrophy. In addition, presynaptic dopaminergic integrity of patient 2 was deteriorated in the motor subregions which was consistent with gray matter atrophy.

Conclusion: These findings provide evidence that C9orf72 repeat expansions could result in degeneration and dopaminergic dysfunction of the striatal motor subregion, which contributed to parkinsonism in FTDP.